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EPIDEMIC DIARRHEA OF THE NEWBORN

I. CLINICOEPIDEMIC, PATHOLOGIC AND THERAPEUTIC ASPECTS

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During August 1938, an epidemic of diarrhea of the newborn occurred in the nursery of a general hospital. This was the third such epidemic observed in this hospital since its opening, in 1924. The one occurring in December 1926 was carefully studied for the usual dysentery bacilli, but none were isolated, and no other reasonable etiologic explanation was found. The epidemic occurring in October 1934 was similarly studied, with the same negative results.

USE OF THE TERM "EPIDEMIC DIARRHEA OF THE NEWBORN"

There is no clearcut understanding as to just what is meant by the term "epidemic diarrhea of the newborn." It is our belief that the term should not be applied to those cases of obviously general sepsis with diarrhea as a prominent symptom, such as were described by Blatt and Wolf.[1] On the other hand, one should not include those fairly frequent simple parenteral infections of newborn infants in which the diarrheal symptoms present are secondary. It is generally recognized that diarrheal symptoms may accompany systemic infection, whether by bacteria or by viruses, and that such a diarrhea is not the result of an infection of the gastrointestinal tract, such as that which accompanies invasion by the dysentery bacillus or by other enteric pathogens. There can be no doubt that there is considerable confusion in the use of the term today. Certainly not all of the cases described in the literature in which diarrheal symptoms appeared during the neonatal period should be classified as

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1. Blatt, M., and Wolf, A. A.: Sepsis of the New-Born Infant, J. Pediat. **14**:695, 1939.

belonging to this group of probably specifically caused infections of the newborn.

We are convinced that there is a definite difference between the bacillary dysentery of newborn infants as we have observed it and the condition which we encountered in the three epidemics mentioned, though in occasional instances there may be a marked similarity in the clinical pictures and to the epidemiologic patterns.

We believe that the term "epidemic diarrhea of the newborn" should be used only when speaking of the same clinical and epidemiologic picture as that studied and described by Rice, Best, Frant and Abramson.[2] The epidemic nature of the infection is probably its most characteristic feature; so until the etiologic basis of the condition is better explained, this term and this application seem preferable.

BACILLARY DYSENTERY OF NEWBORN INFANTS

The occurrence of bacillary dysentery among newborn infants, with positive stool cultures and with blood, pus and mucus in the stools, has not been infrequent in this and in other local hospitals, particularly during those years when the general incidence of this disease was much higher than recently. Bacillary dysentery among newborn infants has been characterized by its mild clinical manifestations, a not particularly severe or watery diarrhea, a low death rate and a tendency to a persistent low grade postinfection indigestion. The onset has usually occurred sometime after the first seven days of life, seldom earlier, and the clinical manifestations, as a rule, have been most in evidence ten to twenty days after birth or later. The usual history has been that for from twenty-four to seventy-two hours before leaving the hospital the infant had had a few loose stools, perhaps with blood and pus, without other evidence of illness being noted. The active clinical manifestations have been observed most generally after the infant had left the hospital. In striking contrast are the generally earlier age at onset, the greater severity and the higher morbidity and mortality rates of epidemic diarrhea of the newborn as it has been observed in the three epidemics in this hospital.

Admittedly, we have never encountered the Shiga strain of dysentery bacillus in these cases. The Flexner strain has been the one generally found, although some of our unidentified strains may have been of the Sonne type. This seems likely because on a few occasions late changes in sugar splitting were noted, though at the time this significance was not appreciated. Certainly these bacilli were not of the Flexner or the Shiga type.

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2. Rice, J. L.; Best, W. H.; Frant, S., and Abramson, H.: Epidemic Diarrhea of the New-Born: I. Preliminary Considerations on Highly Fatal Diarrhea of Undetermined Etiology Among New-Born Babies in Hospital Nurseries, J. A. M. A. **109**:475 (Aug. 14) 1937.

EPIDEMIC OF AUGUST 1938

The epidemic observed in August 1938 appeared to be in every respect similar to the first two, except that there were more infants involved and that the average clinical picture was more severe.

Our results from checking over those in contact with the patients for evidences of intestinal infections which might have been of significance were entirely negative. There had been no diarrhea disorders among the mothers or nursery workers; however, their stools were never cultured.

A consideration of general systemic disorders or infections other than those of the gastrointestinal tract was not such a simple matter, and our evidence, while pointedly suggestive, is not as positive as one might desire.

The first and second epidemics had occurred at a time when there was within the community an unusual prevalence of what may be termed with appropriate limitations "acute epidemic influenza."[3a] The prevalence of this condition was accompanied each time by a significant excess of deaths from disorders of the respiratory tract, as well as by an increase in morbidity, particularly among infants.[3b]

Since there was a similar unusual incidence of what appeared to be genuine influenza and of influenzal pneumonitis among the members of the community who were not infants at the time of the third epidemic of diarrhea among the newborn infants and in spite of the fact that it occurred in a warm August, the question arose as to whether there might not be some causal relation between this disease and the coexisting epidemic of diarrheal disorders among newborn infants. The concurrence of the two diseases seemed to us more than a coincidence. In this connection, it is interesting that Dummer, Lyon and Stevenson,[4] while studying an epidemic of benign lymphocytic meningitis in Cincinnati during the summer of 1935, observed that there were at the same time in the nurseries for newborn infants of several hospitals cases of severe diarrhea, with great toxemia and high mortality rates prevailing.

Of the 25[5] mothers lying in during the period of the 1938 epidemic, 8 had at some time during their stay in the hospital temperatures in excess of 100 F. Of these, 6 had elevations of temperature in excess

3. (*a*) Lyon, G.: Epidemic Influenza, in Blumer, G.: Practitioner's Library of Medicine and Surgery, New York, D. Appleton-Century Company, Inc., 1935, vol. 7, p. 259. (*b*) Lyon, G. M.: Health Careers of Normal Children, unpublished data. Data from Bureau of Vital Statistics, West Virginia State Department of Health.

4. Dummer, C.; Lyon, R. A., and Stevenson, F.: Benign Lymphocytic Meningitis, J. A. M. A. **108**:636 (Feb. 22) 1937.

5. Four had stillborn infants or other noteworthy terminations of pregnancy.

of 101 F., and of these, the temperatures of 3 exceeded 102 F. The explanations for these elevations given by the many different physicians of the general obstetric service were variable. Among the conditions suggested were pyelitis, infected kidney, retained lochia, "milk coming in," influenza and grip, most of which did not aid in explaining the epidemic disease among the newborn infants.

REPORT OF A CASE

The mother of the first newborn infant to be attacked by this malady (baby Elbert N.) was not well on admission.[6] She had an indefinite grippal illness for the seven days preceding her admission to the hospital, which had caused her to miss her regular weekly antepartum visit to her obstetrician. As she lived at some distance in the country, no reliable clinical observations are available for this period. She came to the city in labor and was admitted to the hospital at midnight on August 13, with a temperature of 100.2 F. On admission, she gave a history of having had the week prior an indefinite grippal sickness, with malaise, aches and pains, chilling and some respiratory discomfort but no diarrhea. On the day after admission (August 14) she had a temperature of 100.4 F. at noon. A cesarean section was performed at 2:30 p. m., and a temperature of 101 F. was recorded at 4 p. m. During the next five days (August 15 to 19) her temperature ranged from 99.2 to 100.4 F., and she frequently required sedatives and inhalations to relieve her dry, unproductive cough. Her stools were all soft or formed. On admission, redness of the oropharynx was noted. Although she was given a private room, her infant was placed in the general newborn infants' nursery and regularly after the first twenty-four hours was taken to her every four hours to nurse and then returned to the general nursery. Little attention was paid to the history of the mother's grippal symptoms. This was perhaps in large measure due to the fact that the illness occurred during a warm August when grip or infections of the respiratory tract seem to attract less attention and when gastrointestinal upsets seem to be generally more common.

During the first five days (August 14 to 18) the infant had breast feedings, water and a modified cow's milk formula; his weight increased from 7 pounds 3 ounces (3,260 Gm.) at birth (August 14) to 7 pounds 8 ounces (3,402 Gm.) on the sixth day (August 19), at which time, although no abnormal stools were noted and there was no dehydration, the temperature was 101.2 F. at 8 a. m. At midnight of the eighth day the temperature was 103.4 F., the infant was irritable and the stools were frequent, thin and yellow. The physician who had delivered the infant requested a pediatric consultation. Until this time, the infant's illness had hardly been recognized, and there had been no pediatric supervision.

The pediatrician described the pharynx and both ear drums as red and injected and the fontanel as bulging moderately. The infant was hyperesthetic and obviously seriously ill. A physiologic solution of sodium chloride was administered subcutaneously, and fluids were forced by gavage. In spite of this, within a few hours the infant had a convulsion, became cyanotic and gave evidence suggestive of both intracranial hemorrhage and infection of the respiratory tract. A further indication of the presence of an unusual infection of the surface mucous membranes was that besides neo-silvol drops for the nose the pediatrician had ordered phenol and glycerin for the ears, unusual medication in pediatric practice

6. Dr. Warren Parsons gave permission to publish the data on baby Elbert N.

for a newborn child. The roentgenogram of the chest was reported by the roentgenologist as "suggestive of pneumonia, with a pus or mucus plug in the right main bronchus."

Calcium gluconate, in solution, was given intramuscularly, while 70 cc. of a physiologic solution of sodium chloride was given subcutaneously and 18 cc. of citrated whole blood from the father was injected into the buttocks in an attempt to arrest any intracranial bleeding.

During the next twenty-four hours, in spite of forcing fluids, the child's weight decreased by 12 ounces (340 Gm.), that is, from 7 pounds 5 ounces (3,317 Gm.) to 6 pounds 9 ounces (2,977 Gm.). Stools were passed with increased frequency. Cyanosis continued, and the infant behaved in almost every respect as if he had had an intracranial accident with hemorrhage. Besides, there were unmistakable evidences of infection of the surface mucous membranes, and the stools were suggestive of so-called epidemic diarrhea of the newborn.

The results of examination of the blood, which were essentially the same as those encountered in the subsequent cases, were reported from the clinical laboratory of the hospital as follows: The hemoglobin content (Sahli) was 113 per cent (17.6 Gm. per hundred cubic centimeters). There were 5,040,000 erythrocytes and 16,700 leukocytes per cubic millimeter. Of 100 leukocytes, 45 were polymorphonulears, of which 26 were segmented forms, 6 juvenile forms and 13 stab forms; 50 were lymphocytes, 3 monocytes and 2 early forms.

In spite of the repeated administration of dextrose, physiologic solution of sodium chloride and oxygen, the patient died at 1:55 p. m. on the tenth day of life, the temperature having ranged from 102.6 to 103.6 F. during the last thirty-six hours. The unhappy failure to remove the infant from the general nursery to an isolation nursery until 10 a. m. of the tenth day of illness, that is, just four hours before his death, hardly needs emphasis here. Unfortunately, permission for autopsy was refused.

SPREAD OF THE EPIDEMIC

After the death of the first patient, explosively and with every one caught off guard, there occurred within the general newborn infants' nursery successive cases of epidemic diarrhea, so that of the 21 newborn children possibly exposed, only 6 escaped. Of the 6 escaping, 2 left the hospital soon after the beginning of the epidemic period, and 2 were born after the institution of isolation and were kept entirely away from the nursery in other parts of the hospital, and were removed within forty-eight hours to their homes. Fortunately, there were not many infants in the general nursery at the time.

CLINICAL FEATURES

An outstanding clinical feature of most of the cases seen in this epidemic was that while the infants had diarrhea, that is, frequent, small, thin stools, it was not of the voluminous watery type which during the early stages so rapidly dehydrates older infants suffering from some of the infectious diarrheas. The first few loose stools tended to be somewhat watery, but thereafter the individual stools were consistently small in amount, although they ranged in number from ten to thirty a

day. In reality, after the first twenty-four to forty-eight hours, they were generally but small spots of mucus with some yellowish or greenish discoloration.

By giving orally increased amounts of dextrose and physiologic solutions of sodium chloride to those it was feared might be stricken because of known exposure and by early resorting to subcutaneous administration of a physiologic solution of sodium chloride at the first sign of illness, it was generally possible to prevent even moderate dehydration. In most of the infants a distinct redness, with injection, of the mucous membranes of the oropharynx and of the conjunctivas was noted. In none except the first infant to be stricken was there any purulent discharge from the nose or throat.

After approximately twenty-four to forty-eight hours of moderate and not excessively dehydrating looseness of stool the infants with the more severe infections became suddenly and acutely prostrated, had high temperatures and lost from 8 to 12 ounces (227 to 340 Gm.) in weight during the succeeding twenty-four to forty-eight hours, with no apparent corresponding dehydration or remarkable loss of fluid by bowel. In general, the stools tended to become loose before the elevation of temperature was observed.

The temperatures of few of the patients with the more severe illnesses failed to reach 102 F., with the majority exceeding 103 F. and some 105 F. Most of the infants with the severe symptoms after five to six days of apparently normal behavior had some loose stools, then convulsions and pronounced cyanosis. They had symptoms not primarily of respiratory or intestinal difficulties but of intracranial involvement, so that intracranial hemorrhage was suspected as the main cause of death of the first 2 to die. In all 5 of those who died and in all 4 of those with severe symptoms who survived, the severity of the symptoms apparently referable to the central nervous system was remarkable.

OBSERVATIONS AT AUTOPSY

Postmortem examination of 3 of the next 8 newborn infants to become acutely ill explained many of the symptoms. The severe generalized edema of the brain was undoubtedly an important, if not the most important, pathologic observation. It was not the edema so commonly observed in patients with severe acute infections or bacillary dysentery; it was a severe edema, with remarkable flattening of the convolutions. This edema undoubtedly produced the symptoms which simulated those of intracranial hemorrhage. The entire brain appeared to have been set on by a severe toxin or by an active neurotropic virus. In the brains of 2 older children we have observed, the Shiga strain of dysentery bacillus, with its powerful neurotoxin, had produced much

the same appearance grossly. However, we felt we could safely rule out such bacillary infections, for we encounter many cases of bacillary dysentery and are familiar with its manifestations. As previously stated, we did not recover any form of Bacillus dysenteriae from any of the patients, before or after death.

In the brain, as in most of the other organs, a remarkable tendency to hemorrhage was observed. The hemorrhages were of pinpoint size, and in no instance were they extensive. They were particularly numerous in all the tissues of the central nervous system and were not limited to the cortex. The blood vessels seemed to be friable, and hemorrhage was more by extravasation and diapedesis than by rupture of the vessel wall. In some sections there was some perivascular round cell infiltration.

The appearance of the mucosa of the large and small intestine in 2 of the infants is best described as resembling that which would be produced by washing a dissolving chemical through the mucosa-lined tube, so marked was the denuding of the mucosa. There were no membranes or mucus casts within the intestines, although the appearance of the mucosa of 1 infant did suggest somewhat the presence of a catarrhal infection. The atony of the intestines was remarkable. The lymphatic patches of the intestines were not unusual, although the mesenteric glands were moderately enlarged and hyperplastic, an unusual observation in newborn infants. There were hemorrhages beneath the mucosa, minute but numerous.

Microscopically, there was no cellular infiltration of the mucosa or serosa. There was no evidence of bacterial life or of bacterial invasion by the usual methods on either gross or microscopic observation. Cultures for the usual pathogenic enteric organisms were in each instance negative.

The cerebral edema, the thinning and atony of the intestines and the hemorrhagic tendency, particularly intense in the brain and intestines but present to a lesser extent in other tissues, were the outstanding pathologic observations. In 1 instance, the lungs had areas of hemorrhagic pneumonitis or "chemical pneumonia," similar to those found in patients early in the influenza epidemic of 1918 and not greatly dissimilar to the lesions observed in the lungs of dogs exposed by one of us to poisonous war gases in the summer of 1918 and studied pathologically by Wislocki, Finney and Winternitz.[7] Winternitz[8] has recorded the

7. Wislocki, G.; Finney, W., and Winternitz, M., working in Medical Research Division, Bureau of Mines and later Chemical Warfare Service, U. S. A., American University, Washington, D. C., May-September 1918.

8. Winternitz, M. C.: The Pathology of War Gas Poisoning, New Haven, Conn., Yale University Press, 1920. Winternitz, M. C.; Wason, I. M., and McNamara, F. P.: The Pathology of Influenza, ibid, 1920.

similarity of the lesions in such lungs to those in the lungs of patients dying from influenza in the epidemic of 1918.

The autopsies were performed by Dr. F. C. Hodges, in 1 case immediately and in the others one and four hours, respectively, after death. The bodies were in a good state of preservation; so the pathologic observations were not simply spontaneous postmortem changes.

USE OF CITRATED WHOLE BLOOD FROM A PATIENT CONVALESCING FROM INFLUENZA

Because there had been a coincident epidemic of influenza with each of the three epidemics of diarrhea of the newborn, it was thought that in spite of certain important contraindicating considerations to give citrated whole blood obtained from a patient lately convalescing from influenza to a newborn infant critically ill with the diarrheal disease might not be too irrational a procedure. The matter was discussed with Dr. W. N. Rowley, who had had previous experience with convalescent influenza serum in the treatment of influenza at the Chelsea Naval Hospital in 1918. Through his assistance, it was possible to obtain blood from an adult who was just completing convalescence from a severe attack of uncomplicated influenza. Her illness had been characterized by high fever, erythematous rash on the mucous membranes of the oropharynx and the conjunctivas, frequent profuse sweating, malaise, aches and pains, some respiratory and intestinal discomfort and well marked leukopenia, with relative lymphocytosis. Her protracted convalescence, with vasomotor instability, like these symptoms, was characteristic of influenza.

It was thought that blood from this patient might be of assistance in arresting the further extension of the disease encountered in the newborn children.

Into the gluteal regions of a critically ill infant (R. O.) 30 cc. of this citrated convalescent whole blood was injected on the second day of severe illness (chart 1). The apparent result of administering the citrated blood was so remarkable that when a few days later 2 more cases of similar severity occurred the procedure was repeated. So similar were the clinical manifestations and so similar their remarkable improvement that they will be described together, although the charts are presented for study individually (charts 1, 2 and 3).

Each of the 3 newborn infants so treated, after a perfectly normal and uneventful previous history, had a sudden onset of symptoms, with diarrhea, extreme and early prostration not accompanied by apparent dehydration, a temperature in excess of 105 F., generalized convulsions, cyanosis, moderate vomiting and attempts to vomit. Into the buttocks and the thighs of each infant 30 cc. of citrated convalescent whole blood was injected. The clinical response was so dramatic in each instance

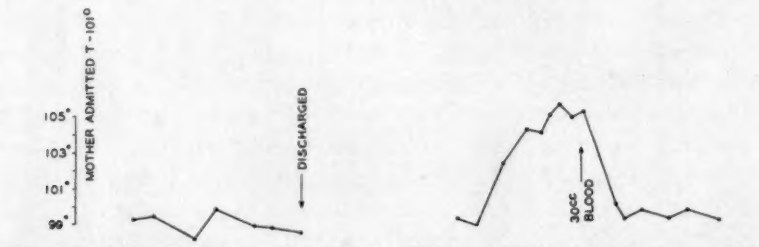
WEIGHT	8-4	8-4	8-0	8-7	8-9	8-11	8-12	8-14	8-10	8-0			7-10
	NORMAL MALE								APATHY PHARYNX RED DIARRHEA CONVULSIONS	CYANOSIS DIARRHEA	DIARRHEA	DIARRHEA	DIARRHEA
	DEXTROSE	BREAST SIMILAC	BREAST SIMILAC	BREAST SIMILAC	BREAST SIMILAC	BREAST SIMILAC	BREAST SIMILAC	BREAST SIMILAC	SAL. SOL. LACTIC ACID MILK SAL. SOL.	SAL. SOL. LACTIC ACID MILK	LACTIC ACID MILK	LACTIC ACID MILK	LACTIC ACID MILK
AGE	1	2	3	4	5	6	7	8	9	10	11	12	13
DATE	17	18	19	20	21	22	23	24	25	26	27	28	29

Chart 1.—Clinical data for baby Robert O. Similac is a spray-dried homogenized mixture of fresh skimmed milk of which the calcium caseinate has been converted to sodium and potassium caseinate, additional lactose, potassium, milk fat, olive oil, coconut oil and cod liver oil.

WEIGHT	6-15	6-11	6-10	6-12	6-13	7-2	7-6	7-8	7-9	7-1	7-1	6-13	6-13
	NORMAL FEMALE							PROBABLY SOME THIN STOOLS	DIARRHEA - YELLOW WATER PHARYNX INJECTED REFUSED FEEDINGS CYANOTIC - 10 P.M.	CONVULSIONS - 2 A.M. CYANOSIS DIARRHEA	DIARRHEA	DIARRHEA	DIARRHEA
	DEXTROSE BREAST	BREAST SIMILAC	BREAST SIMILAC	BREAST SIMILAC	BREAST SIMILAC	BREAST ONLY	BREAST ONLY	BREAST ONLY	SAL. SOL. SAL. SOL.	SAL. SOL. LACTIC ACID MILK SAL. SOL.	SAL. SOL. LACTIC ACID MILK	SAL. SOL. LACTIC ACID MILK	SAL. SOL. LACTIC ACID MILK
AGE	1	2	3	4	5	6	7	8	9	10	11	12	13
DATE	22	23	24	25	26	27	28	29	30	31	1	2	3

Chart 2.—Clinical data for baby Don S.

as to be practically absurd. At the same time is was undeniable. In but a few hours the temperatures were remarkably lower, and the children were clinically immeasurably improved. Their treatment was otherwise not particularly remarkable. They were given physiologic solution of sodium chloride subcutaneously and 10 per cent dextrose in physiologic solution of sodium chloride by gavage, and beginning twenty-four hours after the administration of the blood they were given by gavage Merrell-Soule brand whole lactic acid milk, to which dextrose to make a 10 per cent solution had been added. Although there was a remarkable improvement in their conditions early, their prostration continued



WEIGHT	6-11	6-11	6-11	6-11	6-13					6-0	6-0	5-11	5-9
		NORMAL FEMALE					DIARRHEA	REFUSED FOOD DIARRHEA IRRITABLE	CONVULSIONS CYANOSIS DIARRHEA PHARYNX RED	CONVULSIONS CYANOSIS PROSTRATED DIARRHEA	DIARRHEA	DIARRHEA	DIARRHEA
	WATER	WATER BREAST	WATER BREAST	BREAST	BREAST	BREAST	BREAST	BREAST SAL SOL	SAL SOL LACTIC ACID MILK SAL SOL	SAL SOL LACTIC ACID MILK	SAL SOL LACTIC ACID MILK	SAL SOL LACTIC ACID MILK	SAL SOL LACTIC ACID MILK
AGE	0	1	2	3	4	5	6	7	8	9	10	11	12
DATE	22	23	24	25	26	27	28	29	30	31	1	2	3

Chart 3.—Clinical data for baby Clyde S.

to be of such intensity during the first three or four days that gavage was necessary for administration of fluids or foods. By gavage they received 2 ounces (59 cc.) of the formula every four hours and, in addition, dextrose and physiologic solution of sodium chloride between feedings. Vomiting was encountered early, but it was never excessive or severe and was not an important handicap. The tendency to pass small frequent stools and the lack of digestive ability, of course, persisted, but after seven to ten days the infants required little active medical supervision.

The urinary output of each of the 3 patients was excellent throughout, and there was remarkably little loss of fluid by bowel, although the first week there were twenty to thirty small stools daily and the napkins for another fifteen to twenty days contained decreasing amounts of

mucus and increasing amounts of fecal material. Neither forcing the feedings by gavage nor adding the 10 per cent of dextrose to the feedings aggravated the diarrhea, as some might anticipate. Dehydration did not develop and was apparently not an all-important factor in the production of the severe symptoms. The infants did not show evidence of acute fluid imbalance to the degree one would expect from their critical state. Although the carbon dioxide–combining power of the blood was not studied, the clinical picture did not suggest acidosis, and we believe the alkali reserve was at no time seriously affected. This may have been in part due to the persistent use of subcutaneous injections of physiologic solution of sodium chloride and to the early and frequent administration of suitable fluids and dextrose by gavage. Certainly these 3 infants were as critically ill as they could be and yet recover. The charts indicate their clinical course.

We should like to point out that the feedings given these newborn children during the first week of life were not those they would have received under pediatric supervision. Although we are opposed to this practice of forcing supplemental artificial feeding during the first week of life, we do not believe, as may be suggested by some, that this overfeeding with artificial foods was the cause of the epidemic diarrhea, for newborn children in this hospital have been fed in this manner sufficiently long for us to be sure this was not a causative factor. Other disorders are caused by this procedure, but they are not of the epidemic diarrheal type. The majority of the infants attacked were breast fed. Most of these received too little supplementary feeding for it to be of significance, other than as a possible source of infection. Three of the infants attacked had only breast milk and water, with no additional artificial feedings. The infant whose data are given in chart 3 had only breast milk and water and spent only seventy-eight hours in the hospital before being removed to his home.

Comment.—What in the citrated whole blood, if anything, aided the children's recovery we are not prepared to say. As compared with some of the other children who were certainly not nearly as critically ill, these children made remarkable recoveries and had a shorter, less stormy clinical course once the blood was administered.

Essentially the same general pediatric measures were used for all the infants ill during the epidemic, that is, the protection of fluid balance, the administration of dextrose, the employment of rational feeding and the avoidance of laxatives.

Three of the patients received transfusions of citrated whole blood from normal adults. One of these recovered, but only after a protracted clinical course and repeated transfusions.

Besides these patients who received blood transfusions, the first infant to be attacked had injected into his buttocks 18 cc. of citrated

whole blood from his father at a time when it was felt that the infant had a cerebral hemorrhage. This did not materially change his condition, for death occurred within forty-eight hours.

The ineffectiveness of normal adult blood was observed in these cases. This is all the more interesting in connection with the apparently successful use of the convalescent blood in the other cases. While in no sense providing an adequate control for the successfully treated patients, this limited experience provides food for thought.

Of 16 infants attacked, 5 died and 11 recovered. Of the 11 recovering, the illness of 5 was severe, of 2 moderately severe and of 4 mild. Of those recovering, the ones who received citrated blood intramuscularly were clinically the most critically ill. None of the others who recovered had convulsions, an elevation of temperature above 103 F. or severe cyanosis, while all of those that died did have these symptoms. We believe the 3 newborn infants treated with the convalescent blood would not have done so well had the blood not been administered. We believe the procedure is worth repeating by others in similar circumstances.

RÉSUMÉ OF CLINICOEPIDEMIOLOGIC DATA ON THE THREE NEWBORN CHILDREN TREATED WITH CONVALESCENT BLOOD AND ON THEIR MOTHERS

CASE 2.—*The Mother.*—Mrs. R. O., a primipara, was admitted to the hospital on August 17. There had been some general aches and pains and a slight elevation of temperature on the day of admission. As this was her first pregnancy, she was confused as to the significance of her symptoms and assumed they were just a part of "having a baby." No notation of her having been ill recently was made when she was examined on admission, although her temperature was 100.6 F. shortly after admission. This was several hours prior to delivery. Her maximum temperature was 101 F. on August 21, 100.6 F. on August 23 and 103.5 F. on August 25, with chills on the last day. During this time, although she had chills and fever, she had no complicating disturbances in the plevis or the urinary tract. On August 25 she also had grippal aches and pains and an inflammation of the oropharynx, all of which taken together seemed to justify a diagnosis of influenza. Her convalescence was short, uncomplicated and suggestive of a mild influenzal infection.

It is impossible to say whether Mrs. R. O. had influenza when she was admitted to the hospital, but it is likely that she showed evidences of it at least from her fifth day in the hospital (August 21). It is impossible to say whether she acquired the infection before or after entering the hospital. Her susceptibility to influenza at this time seems likely, and if she was susceptible her infant probably was also.

The Infant.—A boy, R. O., was delivered spontaneously on the night of August 17, and had no symptoms of moment until August 24, when he refused some feedings, had some thin stools and may have had a slight elevation of temperature. On August 25 he had more loose stools, cyanosis, convulsions and a temperature of 103.5 F., at almost the same hour that the mother was having chills and her peak elevation of temperature to 103.5 F. A pediatric consultation was requested, and on the following day (August 26) he was given citrated whole blood. His

temperature was then 105 F., and his condition was poor. His subsequent history has already been summarized.

Transmission of the Infection.—One wonders whether both the child and the mother may not have acquired their infections within the hospital. The infant was taken to the mother to be fed every four hours, and he may have carried the infection from the nursery to her. On the other hand, it is possible that Mrs. R. O. may have had influenza on admission and that she may have given it to her own infant, just as had Mrs. Elbert N., the mother who was responsible for initiating the epidemic. It seems most likely, however, that the infant of Mrs. Elbert N. gave the disease to baby R. O., for they occupied adjoining bassinets for the most part of the last six days the former was in the general newborn infants' nursery. This six days constituted the initial phase, or incubation period, of the epidemic, but, as is generally the case, this was unrecognized at the time.

CASE 3.—*The Mother.*—Mrs. D. S., a multipara, was admitted to the hospital on August 21 and was delivered spontaneously at 10 o'clock that night. She and her infant were discharged fourteen days after delivery. Her course in the hospital was afebrile throughout, and she presented no evidence of any illness until September 5, two days after she returned home. This was seven days after the onset of the infant's illness. At this time, the mother had an elevation of temperature to 100.2 F., chills, aches and pains, some tracheitis and a slight gastrointestinal upset, with some loose stools. Her prostration was out of all proportion to the apparent severity of her illness. Except for the prolonged prostration, the illness was of short duration and otherwise not remarkable. She was confined to her bed ten days.

The Infant.—D. S., a girl, was born at 10 o'clock on the night of August 21. After spending her first two days in the general nursery (August 22 and 23), she was removed to a small private room, which she shared with baby R. O. for the next three days (August 23, 24 and 25). This was before R. O. began to show the evidences of infection which became apparent on August 25. They were separated on August 25, and thereafter she had a room of her own. She first showed evidence of difficulty on the eighth day after delivery (August 29). Her symptoms were essentially the same as those of R. O. A pediatric consultation was first called on the ninth day (August 30), at which time she had diarrhea, convulsions, cyanosis and a rectal temperature in excess of 105 F. Citrated convalescent blood was given on the tenth day (August 31). The subsequent history has in general already been summarized.

Transmission of the Infection.—The question arises whether the mother might have incurred an infection of this nature from her infant. One cannot say with certainty that there is any connection between them, but it is of interest that the mother's indisposition suggested an influenzal infection and that her own infant was the only known sick person with whom she had had contact.

CASE 4.—*The Mother.*—Mrs. C. S., a multipara, was admitted to the hospital on August 22, with a temperature of 101 F., because according to her physician she had "the grip" and he was apprehensive lest she might go into labor and have trouble. She had a private room on the obstetric floor. Delivery occurred spontaneously at 2 o'clock in the morning on the following day (August 23). Her temperature receded and later rose to 100 F. on August 24. She left the hospital with her infant on the morning of August 26, approximately seventy-eight hours after delivery. After she returned home she seemed to do well until the tenth day

post partum (September 2), at which time she had a recurrence of her influenzal symptoms, with chills and fever. This was followed by rather severe tracheitis, but she was free of any disturbances in the pelvis or genitourinary tract.

The Infant.—C. S., a girl, was delivered at 3 o'clock in the morning on August 23 and was in the general newborn infants' nursery until August 25, when she was removed to a private room away from other newborn infants. She never received anything but water and breast milk. On August 26 she was taken home, and on August 30, the fourth day after leaving the hospital and the eighth day of life, she became definitely ill. A pediatric consultation was held that night, and citrated convalescent blood was given the day following, August 31. The subsequent history was largely uneventful and has already been summarized.

EPIDEMIOLOGIC OBSERVATIONS

In reviewing the observations, one is struck by the fact that at least 2 of these infants (R. O. and C. S.) might have acquired their infections either from their own mothers or from contact with other infants in the newborn infants' nursery. While exposure in this nursery to a virus whose virulence was being rapidly enhanced seems the more likely source of infection, the other possibility must be considered in these 2 cases.

It is also possible that Mrs. D. S. received her apparent influenzal infection from contact with her own child, because her activities and contacts were restricted.

In all 3 instances it seems likely that the mothers had few, if any, effective immune bodies to pass on to their infants. The temperature curves of the mothers and of the infants indicate the course of events was not normal in either and that neither the mothers nor the newborn infants were free of infection.

The interesting similarity between the clinical severity of the infections of the 3 infants treated with convalescent blood and that of the first infant to be attacked (Elbert N.) cannot be overlooked.

The involvement of two such poorly understood clinical conditions as influenza and epidemic diarrhea of the newborn holds much of speculative interest. These observations are presented only as suggesting a possible relation. They are no more than speculative or suggestive.

It is much to be regretted that a thorough study could not be made of the clinical histories of all the infants involved in the last epidemic. For many reasons it was not possible to include them and all their contacts at home, parental or otherwise, in the study.

It may be that the most characteristic picture occurs only when the environmental situation is just right, as for instance when a virus or other infective agent relatively virulent for newborn children is introduced into the general nursery, where it quickly has its virulence even further enhanced by rapid passage through the intimate contact within the nursery. Then the explosive outbreak appears and does not subside

until all exposed susceptible infants are attacked. Indeed, it seems likely that a susceptible adult may respond to exposure to the same infective agent by a simple influenzal or grippal illness of slight intensity, perhaps so slight as to be overlooked entirely.

Individual cases of this malady probably do occur outside newborn infants' nurseries and go unrecognized, because an individual case would probably not be properly recognized. The absence of susceptible newborn infants in the proximity of the single isolated case may prevent the characteristic rapid passage with enhancement of the virulence of the virus and subsequent development of the clinicoepidemic picture considered characteristic.

We are familiar with the common occurrence of intestinal infections in infants in the past. We have been impressed to some extent with the gravity of their occurrence in the neonatal period, yet we have known little about their specific causes. Now that the filth-borne infections of the typhoid-dysentery type are better recognized and better controlled, it is not at all unlikely that we shall recognize other types of generalized infections, among them influenza, which can produce a clinical picture closely simulating that of the older type of infections of the intestinal tract. It may be, indeed, that such cases occurred commonly in the past during epidemics or pandemics of influenza and were considered as evidences of simple gastrointestinal infection or perhaps as "parenteral infections." It was about the time of the 1915-1921 epidemic of influenza, which reached its peak in the pandemic of 1918, that the term "parenteral infection" was introduced as an explanation for simple vomiting and diarrhea with fever. It was during the following decade that it had its greatest vogue. Those who remember the frequent occurrence of this symptom picture at that time are impressed with the relative infrequency with which it is now encountered. The explanation of this interesting change is not clear, yet it is a frequent topic of discussion among pediatricians of extended experience when they gather for their special meetings.

We recognize the difficulties in speaking of influenza as a distinct and definite clinical entity, because its most characteristic features are clinicoepidemic. We recognize also that there are equally grave difficulties attendant on the use of the term "epidemic diarrhea of the newborn," for the most characteristic features of that disease, too, are distinctly clinicoepidemic. We have attempted to avoid using either term carelessly or loosely. Unfortunately, no one can speak of either with clear definition and accuracy.

We have described some observations which, on purely epidemiologic and clinical grounds, suggest a possible causal relation between epidemic influenza and, in some instance at least, epidemic diarrhea of the newborn.

Can epidemic diarrhea of the newborn at times be the expression of influenza virus infection? If so, can an antivirus convalescent serum be effective for newborn children, although it appears to be ineffective for the older child or the adult? From our observations no conclusions can be drawn, but they are of speculative interest, and some of them may be of fundamental importance.

SUMMARY

We have described some features of the three epidemics of diarrheal disorders which come under the general heading of "epidemic diarrhea of the newborn."

We do not believe that they were due to a primary bacterial infection of the gastrointestinal tract, particularly with any of the usual enteric pathogens, including the several strains of B. dysenteriae, or that they are caused by an enterotoxic staphylococcus.

The epidemiologic characteristics of the epidemic of 1938 have been described in detail.

An unusual prevalence of clinical influenzal infections within the community during all three epidemics is noted. Pathologic observations characteristic of uncomplicated influenza were noted in the community during the second and third epidemics described.

That this malady is an expression of infection with influenza virus in the newborn is suggested but by no means proved.

Citrated whole blood from a patient recently convalescent from clinical influenza seemed to have had a markedly beneficial effect on 3 of the most severely ill infants. Normal adult blood had no such effect on the 3 other patients to whom it was given.

Clinical observations are presented which suggest that a mother may be infected by her own ill infant and that her response to the infection may be a clinical influenza.

Emphasis is placed on the fact that, whatever the infective agent, its rapid passage through the physiologically and immunologically immature infant through the unusually intimate contact obtaining within the general newborn infants' nursery makes it likely that an infective agent relatively commonly encountered among the general population may, with the favorable opportunity thus afforded, be so enhanced in virulence that it is responsible for the clinicoepidemic picture recently described as "epidemic diarrhea of the newborn."

It is possible that such cases may occur individually outside of newborn infants' nurseries and go unrecognized because of the distracting presenting symptoms.

Attention is called to the particularly severe neurotropic character of the infective agent or its circulating toxins.

It is suggested that the disease is not new and that it has previously not been recognized because of the general prevalence of gastrointestinal diseases during the time when protection against bacteria in newborn infants' nurseries was from all standpoints greatly inferior to that of today. Then it was probably confused with true primary infection of the gastrointestinal tract because of the prominence of the gastrointestinal symptoms.

The entire report indirectly emphasizes the importance and the attendant difficulties of controlling man-borne infections in the newborn infants' nursery of a general hospital to which a large number of physicians, some specialists in obstetrics and some not, have access. It is a problem worthy of much medical thought and action.

ADDENDUM

Since the report was prepared, one of us (G. M. L.) has observed 2 newborn infants, delivered outside of hospitals in relatively remote rural homes, who died with what appeared to be the same clinical picture of diarrhea, fever and symptoms referable to the central nervous system.

In the first instance (November 1939) the mother had mild, apparently febrile influenza at the time of delivery. Shortly after delivery a marked exanthem of the mucous membranes of the respiratory tract and pneumonitis developed, and she died on the third day post partum, without being hospitalized. At autopsy, there was characteristic nonbacterial pneumonitis, without obstetric complications. Her infant, who did not become ill until the sixth day, was brought to the hospital in a moribund condition on the seventh day and died in convulsions shortly after admission. The clinical course had been similar to that of the patients observed in the newborn infants' nursery. There was besides high temperature, convulsions and signs of involvement of the central nervous system, a diarrheal picture similar to that of the newborn infants sick during the hospital epidemics. Observations at autopsy were similar to those previously described for the other patient. Cerebral edema, without gross hemorrhage was extensive. There was injection of the oropharynx. The lower lobe of the left lung had just such a pneumonitis or "chemical pneumonia" as was shown by 1 of the hospitalized patients at autopsy. The intestines were atonic and otherwise similar to those of the patients from the nursery.

In the second instance (February 1940), at the time of delivery the father and 2 children in the home had what was probably an attack of the then currently prevalent form of influenza. The mother became ill on the third day post partum with what was apparently a characteristic attack of influenza with secondary pneumonia and recovered after a somewhat stormy course. The newborn infant became ill on the sixth day, had symptoms entirely similar to those of the 3 infants given the convalescent whole blood and died on the ninth day. Permission for autopsy was not obtained.

Unfortunately, in neither instance was it possible to give convalescent blood. One infant was moribund on admission to the hospital and died shortly after, and the other died before the convalescent blood could be obtained, taken to the rural home and administered.

This note is added because these observations suggest (1) the possibility that such a clinical picture as that seen in the typical epidemic in the nursery may occur outside such a nursery, (2) the possible relation between the occurrence of such cases, either singly or epidemically, concurrently with a prevailing influenzal type of infection and (3) the desirability of more critically observing newborn infants outside of hospitals when they present clinical pictures similar to those described, particularly when death ensues and autopsies are possible.

There is some good yet meager evidence to suggest that the disease is not confined to newborn infants' nurseries and also that perhaps many of these cases in the past have been erroneously looked on as examples of simple cerebral hemorrhage or other birth injury, or of "septic death" with diarrhea as a symptom. Von Reuss [9] referred to (1) the susceptibility of newborn infants to air-borne infections, including influenza, (2) the occurrence of enteritis as well as catarrhal infections in newborn infants during epidemics of influenza in lying-in hospitals and (3) "septic deaths," which could easily have been in many instances the same disease now referred to as "epidemic diarrhea of the newborn."

In this connection, it is of interest to note that Frant and Abramson [10] have graphically called attention to the fact that in New York city while the diarrheal death rate of infants from 1 month to 1 year of age has dropped steadily during the decade 1926 to 1936, the diarrheal death rate of children from birth to 1 month of age has steadily risen, practically doubling during the same decade. Obviously, this is an important challenge to those who have the wefare of the newborn infant at heart.

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9. Von Reuss, A. R.: Diseases of the Newborn, New York, William Wood & Company, 1922, pp. 291, 487 and 531-537.

10. Frant, S., and Abramson, H.: Epidemic Diarrhea of the Newborn, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1939, vol 1, chap. 28, p. 21.

GRANULOCYTOPENIA

REPORT OF THREE CASES IN WHICH THE CONDITION WAS DUE TO INFECTION AND IN WHICH CHEMOTHERAPY WAS EMPLOYED

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Although three years ago granulocytopenia was a relatively rare condition in childhood, the recent widespread use of chemotherapy has greatly increased its incidence. Kracke,[1] in 1938, thoroughly reviewed the literature on the relation of drug therapy to neutropenic states. He cited 11 cases of granulocytopenia, 9 of them with fatal termination, which resulted from the use of sulfanilamide. In all instances a large amount of the drug was administered over a relatively long period before the condition made its appearance. Because of this fact, he expressed the belief that the granulopoietic depression from sulfanilamide therapy probably differed in mechanism from that which has followed the administration of aminopyrine. Other cases of granulocytopenia due to the use of sulfanilamide have been reported by Cutler and Crane,[2] Pearson [3] and Schecket and Price.[4]

That sulfapyridine (2-[paraaminobenzenesulfonamido] pyridine) would likewise cause leukopoietic depression seemed probable at the time of its introduction because of its close chemical relation to sulfanilamide. One of the earliest reports was made by Johnston [5] who described a case in which granulocytopenia, resulting in death, followed the use of the drug in treatment of puerperal sepsis. Shortly after this, Coxon and Forbes [6] used sulfapyridine to treat a patient with typhoid fever complicated by thrombophlebitis. Their patient recovered despite

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1. Kracke, R. R.: Relation of Drug Therapy to Neutropenic States, J. A. M. A. **111**:1255 (Oct. 1) 1938.

2. Cutler, I. L., and Crane, E. J.: Agranulocytosis Caused by Sulfanilamide, New England J. Med. **221**:231 (Aug. 10) 1939.

3. Pearson, H. E. S.: Fatal Agranulocytosis After Sulphanilamide Treatment, Brit. M. J. **1**:1031 (May 20) 1939.

4. Shecket, H. A., and Price, A. E.: Fatal Granulocytopenia Following Administration of Sulfanilamide, J. A. M. A. **112**:823 (March 4) 1939.

5. Johnston, F. D.: Granulocytopenia Following Administration of Sulphanilamide Compounds, Lancet **2**:1044 (Nov. 5) 1938.

6. Coxon, R. V., and Forbes, J. R.: Agranulocytic Angina Following Administration of M. & B. 693, Lancet **2**:1412 (Dec. 17) 1938.

the fact that the white blood cell count fell to 1,000 per cubic millimeter, with no polymorphonuclears. Hodes and his associates [7] had 5 cases of mild and 1 case of severe granulocytopenia in their series of 71 cases of pneumococcic pneumonia in children in which sulfapyridine was used. A comparative study of the blood and the bone marrow was made in the 3 cases of granulocytopenia reported by Rosenthal and Vogel.[8] In the 1 patient who died there was marked myeloid hypoplasia, whereas in those who recovered there was arrest in maturation of the myeloid elements. Long;[9] Pringle, Dockeray and Mitchell;[10] Dolgopol and Hobart;[11] Barnett and his associates;[12] Christian, Jorgensen and Ellis,[13] and others have described cases which came under their observation.

There is a scarcity of information as to the toxic effect of sulfathiazole (2-[paraaminobenzenesulfonamido] thiazole) on the bone marrow. In a series of 83 cases of pneumonia treated with sulfathiazole, Reinhold and his associates [14] reported no instance of depression of the granulocytes.

Although the great majority of these cases cited from the literature appear as clearcut instances of toxicity due to drugs there are a few in which it is evident that the original infection, as well as the drug, was influential in producing the depression of the bone marrow. Coxon and Forbes pointed out in their report of a case of typhoid fever that although the action of the drug was definitely involved in causing the granulocytopenia, the natural leukopenia associated with the disease could be considered a contributing factor. Dolgopol and Hobart expressed the belief that in 2 of their cases there was possibly a combined action of the original infection and the drug on the bone marrow.

Occasionally granulocytopenia has been associated with infection in instances in which no drug could be implicated. In a case of infection

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7. Hodes, H. L.; Stifler, W. C.; Walker, E.; McCarty, M., and Shirley, R. G.: The Use of Sulfapyridine in Primary Pneumococcic Pneumonia and in Pneumonia Associated with Measles, J. Pediat. **14**:417 (April) 1939.

8. Rosenthal, N., and Vogel, P.: Granulocytopenia Caused by Sulfapyridine in Children, J. A. M. A. **113**:584 (Aug. 12) 1939.

9. Long, P. H.: Sulfapyridine, J. A. M. A. **112**:538 (Feb. 11) 1939.

10. Pringle, B.; Dockeray, G. C., and Mitchell, R. H.: Agranulocytosis Following Sulphapyridine Therapy, Brit. M. J. **1**:212 (Feb. 10) 1940.

11. Dolgopol, V. B., and Hobart, H. M.: Granulocytopenia in Sulfapyridine Therapy, J. A. M. A. **113**:1012 (Sept. 9) 1939.

12. Barnett, H. L.; Hartmann, A. F.; Perley, A. M., and Ruhoff, M. B.: Treatment of Pneumococcic Infections in Infants and Children with Sulfapyridine, J. A. M. A. **112**:518 (Feb. 11) 1939.

13. Christian, H. S.; Jorgensen, G. M., and Ellis, C.: Treatment of Pneumococcic Infections in Children with Sulfapyridine, Am. J. Dis. Child. **59**:1 (Jan.) 1940.

14. Reinhold, J. G.; Flippin, J. F., and Schwartz, L.: Observations on the Pharmacology and Toxicology of Sulfathiazole in Man, Am. J. M. Sc. **199**:393 (March) 1940.

of the maxillary antrums with Streptococcus viridans described by Walsh,[15] the white blood cell count was depressed to 2,600 cells per cubic millimeter, with no granulocytes. There was no history of any form of chemotherapy or of the administration of aminopyrine or any of the derivatives of barbituric acid. Similar cases have been reported by Richmond,[16] Rutledge and his associates,[17] Jeter [18] and Hunter.[19]

At the Babies Hospital within the past six months 3 patients with granulocytopenia have been observed in whom it appeared that the infection rather than the drug was the cause of the initial depression of the bone marrow. In reporting the cases of these patients particular attention will be paid to the changes in the blood and the bone marrow, the use of pentnucleotide and the effect of chemotherapeutic agents.

REPORT OF CASES

CASE 1.—*Bilateral otitis media, mastoiditis and granulocytopenia; restoration of white cell count to normal after the use of pentnucleotide; recurrence of granulocytopenia after the administration of sulfanilamide and sulfathiazole.*

History.—M. G., a girl 4 months of age, was admitted to the Babies Hospital for the first time with a chief complaint of running of the ears of one day's duration. The parents were well. There were no siblings. No history of blood dyscrasia in the family was obtained. The patient was the result of a normal, spontaneous delivery at full term. The birth weight was 5 pounds 9 ounces (2,523 Gm.). The neonatal period was normal. The patient was fed an evaporated milk formula from birth. Cereal was added to the diet at 3 months and strained vegetables at 3½ months of age. The intake of vitamins was adequate. The infant was perfectly well until two weeks prior to admission, when cough and a cold developed. Because of an increase of temperature, irritability and bulging of the ear drums bilateral myringotomy was done one week later. The left ear stopped discharging three days before admission, and a swelling was noted behind the left ear at about the same time. One week before admission the infant received 0.4 Gm. of azosulfamide (the disodium salt of 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′,6′-disulfonic acid) during a twenty-four hour period. No other chemotherapy was received. At no time was aminopyrine or any of the derivatives of barbituric acid given.

Physical Examination.—The temperature was 100 F. The weight was 5,070 Gm. The patient was well developed and well nourished and looked acutely but not seriously ill. There was purulent discharge from both ears. A moderate amount of swelling and tenderness was present over both mastoid processes, with redness over the left. The nose was normal, and the throat was clear. The lungs, heart and abdomen were normal.

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15. Walsh, T. E.: Agranulocytosis Associated with Maxillary Sinusitis, Arch. Otolaryng. **29**:388 (Feb.) 1939.

16. Richmond, E. L.: Granulocytopenia Following Surgical Sepsis and Treated with Adenine Sulfate, New England J. Med. **221**:267 (Aug. 17) 1939.

17. Rutledge, B. H.; Hansen-Prüss, O. C., and Thayer, W. S.: Recurrent Agranulocytosis, Bull. Johns Hopkins Hosp. **46**:369 (June) 1930.

18. Jeter, H.: Recurrent Agranulocytosis, South. M. J. **32**:878 (Aug.) 1939.

19. Hunter, R. J.: Agranulocytic Angina: Report of a Case Associated with Fracture of the Tibia, Laryngoscope **36**:348 (May) 1926.

Laboratory Data.—The hemoglobin content of the blood (Sahli) was 8.1 Gm. per hundred cubic centimeters; the red cell count was 3,800,000 and the white cell count 6,150 per cubic millimeter, with 10 per cent polymorphonuclears, 57 per cent lymphocytes and 33 per cent monocytes. The urine was normal on repeated examination. The heterophil antibody reaction of the blood was within normal limits. The reactions to the Mantoux (1:1,000) and the Kline test were negative. Blood cultures made on Dec. 14, 1939 and Jan. 6, Jan. 8, Jan. 18 and Jan. 19, 1940 showed no growth. On Dec. 8, 1939 smears showed that 37 per cent of the white blood cells in the material from the ears and 40 per cent of those in the material from the mastoids were polymorphonuclears. Organisms cultured from material from the ears and the mastoidectomy wounds included beta hemolytic streptococcus, Staphylococcus aureus haemolyticus and nonhaemolyticus, Str. viridans and Pneumococcus type I. The levels of sulfathiazole in the blood were: January 20, 2.6 mg. per hundred cubic centimeters; January 21, 1.2 mg.; January 22, 1.8 mg., and March 14, 5.4 mg.

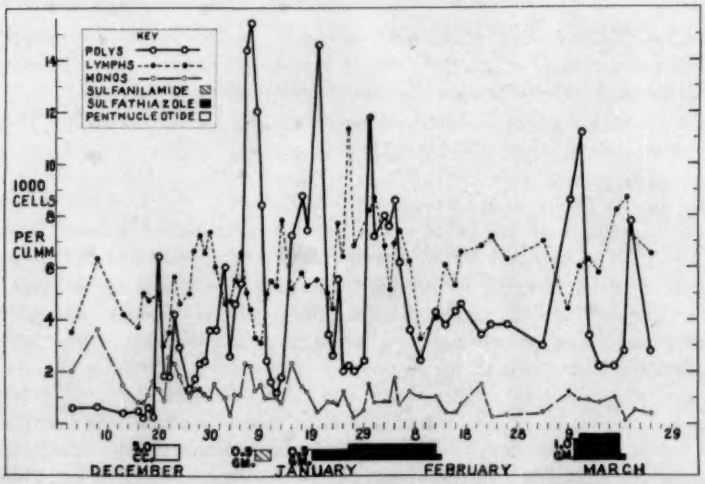

Fig. 1 (case 1).—Variations in the absolute leukocyte count with infection and with administration of drugs.

Course.—Five days after admission simple mastoidectomy was done on the left side. The absolute polymorphonuclear count, which on admission was 600 cells per cubic millimeter,[20] remained at this level despite the presence of active infection. On the sixteenth day in the hospital intramuscular injections of pentnucleotide were begun, 5 cc. being given daily for six days. The polymorphonuclear count rose on the following day to a value exceeding 6,000 cells per cubic millimeter (fig. 1). There was a moderate fall in the white blood cell count after the administration of pentnucleotide was discontinued, but the values never approached those seen before treatment, and the average level came to lie within normal limits (fig. 1). Three weeks after admission, with the temperature still elevated and with

20. The absolute number of polymorphonuclears in children of this age is usually greater than 2,500 cells per cubic millimeter and in the presence of an active infection should exceed this value.

roentgen evidence of bone destruction in the right mastoid process, simple mastoidectomy was done on the right side. Both mastoidectomy wounds were extremely slow to heal, and the discharge from the ears continued to be profuse. Because of this profuse drainage from the ears, adenoidectomy was performed. On the first postoperative day the temperature was elevated and a red, indurated, sharply demarcated area was noted spreading out from the mastoidectomy wound on the left. Cultures of material from the mastoidectomy wound made on the previous day had grown beta hemolytic streptococcus as the predominant organism. Sulfanilamide was started, 0.5 Gm. (0.1 Gm. per kilogram of body weight) being given daily for the next four days. There was prompt recession of the erysipelas, and the temperature fell to normal. During the period of administration of the drug the absolute number of polymorphonuclears fell from 15,400 to 1,600 cells per cubic millimeter. Five days after administration of the drug was discontinued the polymorphonuclear count was 8,855 cells per cubic millimeter, and a new area of erysipelas became manifest. Because further chemotherapy seemed indicated, the patient was given 0.5 Gm. (0.1 Gm. per kilogram of body weight) of sulfathiazole daily. Administration of the drug was continued over twenty-four days, during which time a total of 17 Gm. was administered. Although there was a preliminary depression of the granulocytes, a secondary rise occurred despite continued administration of the drug. Even with prolonged drug therapy purulent discharge from both auricular canals and from the mastoidectomy wounds continued. On the fifty-seventh day in the hospital bilateral revision of the mastoidectomy wounds was performed. By the thirty-fourth postoperative day both wounds were healed, but profuse discharge from the auricular canals continued. Six days later, with the onset of an acute infection of the upper respiratory tract, there was a sharp elevation of temperature. Cultures of material from the throat at this time showed a predominance of Pneumococcus type VIII, and a second course of sulfathiazole was started. One and five-tenths grams of the drug (0.3 Gm. per kilogram of body weight) was given daily for nine days. There was a definite but transient fall in the absolute number of polymorphonuclear leukocytes in the blood (fig. 1). On the one hundred and thirteenth day in the hospital the child was discharged to a convalescent home, with an essentially normal white cell count. Both ear drums had large perforations and were draining slightly at the time of discharge.

CASE 2.—*Acute infection of the upper respiratory tract and granulocytopenia; further depression of leukocytes after administration of sulfanilamide; restoration of white cell count to normal after discontinuance of chemotherapy and the use of pentnucleotide.*

History.—M. R., a girl 1 year of age, was admitted to the Babies Hospital with a chief complaint of cough and fever of two days' duration. The father had died of heart disease one week prior to the infant's first admission to the hospital. The mother was living and well. There were no siblings. No history of blood dyscrasia in the family was obtained. The patient was the result of a normal, spontaneous delivery at full term. Her feeding and intake of vitamins were adequate. There was no meat present in the diet until the age of 10 months. Her appetite was always good and her general condition excellent until the first stay in the hospital, which was from Dec. 2 to Dec. 14, 1939, when a diagnosis of acute purulent ethmoiditis on the right side was made. Culture of material from the throat showed beta hemolytic streptococcus to be the predominant organism.

A course of sulfanilamide was started on the day of admission, and the infant received 0.6 Gm. that day. The following day she received 0.3 Gm. There was

no further chemotherapy and no administration of aminopyrine. Examination of the blood (Sahli), after the child had received 0.6 Gm. of sulfanilamide, showed 9.0 Gm. of hemoglobin per hundred cubic centimeters; the red cell count was 3,600,000 and the white cell count 8,700 per cubic millimeter, with 65 per cent polymorphonuclears.

The second stay in the hospital was from Jan. 2 to Jan. 8, 1940, when a diagnosis of acute tonsillitis, acute pansinusitis, bilateral acute catarrhal otitis media and hypertrophied adenoids was made. The leukocyte count was 9,050 cells per cubic millimeter, with 54 per cent polymorphonuclears. With rest in bed and general supportive measures, the infant's condition rapidly improved. No form of chemotherapy, no aminopyrine and no barbiturates were given.

The third stay in the hospital was from Jan. 28 to March 5, 1940. Twenty days before the third entry into the hospital, the patient began to have a fever and lost her appetite. One week prior to admission she began to cough, and her temperature rose to 105 F. Two days before admission the patient's respirations became labored. Although seen by her private physician on two occasions, she was given no medication except 0.6 Gm. of acetylsalicylic acid.

Physical Examination.—The temperature was 102 F. The weight was 8,780 Gm. The patient was well developed and fairly well nourished and appeared chronically ill. There was no respiratory distress. Both ear drums were red and bulging. There was a watery discharge from the nose. The tonsils were large and red, and the pharynx was injected. The lungs were resonant. There were some rhonchi in the chest, but no rales were heard, and there was no suppression of breath sounds. Examination of the heart and abdomen gave normal results.

Laboratory Data.—The hemoglobin content of the blood (Sahli) was 10.9 Gm. per hundred cubic centimeters; the red cell count was 3,880,000 and the white cell count 2,400 per cubic millimeter, with 38 per cent polymorphonuclears, 33 per cent lymphocytes and 25 per cent monocytes. Results of repeated urinalyses were normal. The reactions to the Mantoux (1 : 1,000) and the Kline test were negative. Blood cultures made on February 3 and February 5 were positive for Pneumococcus type XIV. Cultures of material from the nose and throat showed a predominance of Pneumococcus type XIV. Agglutination tests with the typhoid-paratyphoid group of organisms all gave negative results. The level of sulfathiazole in the blood was 3.5 mg. per hundred cubic centimeters on February 22.

Course.—On admission a diagnosis of otitis media, sinusitis and bronchitis was made. The absolute number of polymorphonuclears on the day of admission was 880 cells per cubic millimeter. During the next eight days there was a rise in the value to 2,240 cells per cubic millimeter, associated with the development of physical signs of pneumonia. A total of about 2.8 Gm. of sulfathiazole was given during the next four days. In addition, 100,000 units of rabbit antipneumococcus serum type XIV (Lederle) was administered. On the fourth day the absolute polymorphonuclear count had fallen to 900 cells per cubic millimeter and administration of the drug was discontinued (fig. 2). The patient was given a transfusion of 140 cc. of citrated blood the next day, but the count continued its downward course, reaching a value of 175 polymorphonuclears per cubic millimeter. Twenty-four hours later, with the count at 54 polymorphonuclears per cubic millimeter, another transfusion of 130 cc. of citrated blood was given, and administration of pentnucleotide was started. For the next four days the infant received daily intramuscular injections of 5 cc. of pentnucleotide. The polymorphonuclear count rose to 316 cells per cubic millimeter on the fourth day and then to 2,500 on the

following day (fig. 2). Associated with the increasing polymorphonuclear count was a transitory appearance of myelocytes in the peripheral blood. Despite discontinuance of administration of the drug and the low white cell count, the infant's clinical condition slowly but progressively improved. Five weeks after admission, the infant was discharged in good health and with a leukocyte count of 6,200 cells per cubic millimeter, of which 56 per cent were polymorphonuclears.

CASE 3.—*Bilateral otitis media treated with sulfathiazole; granulocytopenia resulting from chemotherapy and from infection; restoration of white cell count to normal after injections of pentnucleotide; recurrence of granulocytopenia and recovery without specific therapy.*

History.—W. B., a boy 8 months of age, was admitted to the Babies Hospital with a chief complaint of diarrhea and vomiting of three days' duration. The parents were well. There were no siblings. No history of familial disease or of blood dyscrasia in the family was obtained. The patient was the result of a normal,

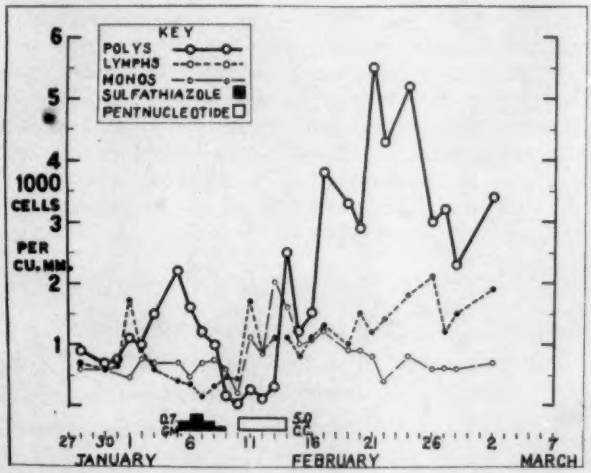

Fig. 2 (case 2).—Variations in the absolute leukocyte count with infection and with administration of drugs.

spontaneous delivery at full term. The birth weight was 7 pounds 6 ounces (3,345 Gm.). The neonatal period was normal. The infant was breast fed for two months and then given a formula of whole cow's milk. Vegetables and fruits were added at 6 months of age. There was no meat in the diet at any time. The intake of vitamins was adequate. The patient had no serious illnesses save severe diarrhea at the age of 15 days, which lasted for about one week. Apparently he had not appeared ill until about four days before admission, at which time he had mild diarrhea, with large green stools. At the same time he began to cough and to vomit. Because of the persistence of the diarrhea and vomiting, admission to the hospital was advised.

Physical Examination.—The temperature was 101 F. The weight was 8,900 Gm. The patient was acutely ill, moderately prostrated and severely dehydrated. Respirations were neither rapid nor typically acidotic in type. The right ear drum was greatly inflamed and bulging, and the left was reddened but not bulging. There was moderate congestion of the nasal passages but no discharge. The tonsils and

the pharynx were moderately injected. The lungs and heart were normal. The edge of the liver was palpable, but the spleen was not felt. Results of the remainder of the physical examination were normal.

Laboratory Data.—The hemoglobin content of the blood (Sahli) was 15.1 Gm. per hundred cubic centimeters; the red cell count was 5,010,000 and the white cell count 13,300 per cubic millimeter, with 60 per cent polymorphonuclears, 25 per cent lymphocytes and 15 per cent monocytes. The urine almost consistently showed a 4 plus reaction for acetone, white cells, red cells and occasional casts. Chemical analysis of the plasma showed: nonprotein nitrogen, 34 mg. per hundred cubic centimeters; dextrose, 101 mg., and carbon dioxide-combining power, 44 volumes per cent. The serum albumin was 3.2 Gm. and the serum globulin 1.4 Gm. per hundred cubic centimeters. The reactions to the Mantoux (1:1,000) and the Kline test were negative. A blood culture made on March 19 showed no growth. The culture of material from the throat made on admission showed approximately equal numbers of beta hemolytic streptococcus and Str. viridans. Cultures of material

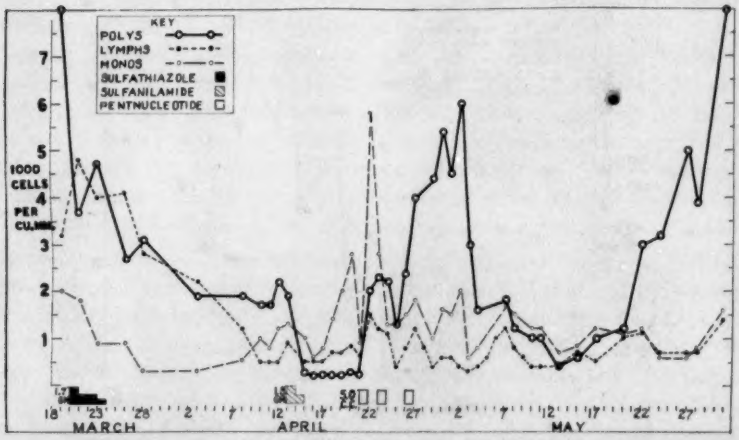

Fig. 3 (case 3).—Variations in the absolute leukocyte count with infection and with administration of drugs.

from the ears showed beta hemolytic streptococcus on March 19 and April 11. Examinations of the stools gave consistently normal results except for an occasional slightly positive reaction to the guaiac test.

Course.—On admission myringotomy was done on the right side, with the release of a large amount of purulent material under pressure. For the first few days in the hospital parenteral administration of fluids was required. On the day after admission administration of sulfathiazole was started. An initial dose of 0.5 Gm. was given, and this was followed by a daily dose of 1.5 Gm. (0.2 Gm. per kilogram of body weight) for four days. The absolute polymorphonuclear count, which on admission had been 7,980 cells per cubic millimeter, fell slowly to 2,650 two days after administration of the drug was discontinued (fig. 3). Despite the fact that no further form of therapy was given, the count continued to fall until it reached a value of 1,530 cells per cubic millimeter on the twenty-second day in the hospital. Because the white cell count appeared to be stabilized at this point and because cultures of material from the ears continued to show beta hemolytic streptococcus, administration of sulfanilamide was begun, 1.8 Gm. being given the

first day and 0.9 Gm. the second day. Thirty-six hours after the administration of the drug was started, the absolute number of polymorphonuclears had fallen to 264 cells per cubic millimeter and administration of the drug was discontinued. A transfusion of 100 cc. of citrated blood was given on each of the two subsequent days. The count failed to change appreciably. Although it had been planned not to give this patient pentnucleotide, it was felt that the failure to improve after transfusion and the general poor condition of the child did not justify the withholding of any treatment that might be beneficial. Associated with three intramuscular injections of 5 cc. each of pentnucleotide over a period of five days, the absolute polymorphonuclear count, which for six days previously had been at an average level of about 300 cells per cubic millimeter, rose to values exceeding 4,000 cells (fig. 3). The day after the first injection of pentnucleotide simple mastoidectomy was performed bilaterally. Moderate destruction of both mastoids was found at operation. The immediate postoperative course was stormy, but by the second postoperative day the temperature had fallen and the child seemed improved. Diarrhea continued to be a problem, as did the progressive loss of weight. After a considerable period the diarrhea was controlled, and the patient slowly began to gain weight. About the ninth postoperative day, the patient contracted a fresh infection of the upper respiratory tract, and associated with this was a progressive drop in the absolute polymorphonuclear count (fig. 3). The mastoidectomy wounds healed slowly, and the auricular canals continued to be moist. Ten days after the onset of the infection of the respiratory tract, the absolute polymorphonuclear count had fallen to 400 cells per cubic millimeter. Without specific therapy, the white cell count slowly but progressively rose to normal.

COMMENT

From a review of the literature and from the cases presented, it is apparent that leukopoietic depression is a toxic effect that may occur as a result of infection or that may be associated with the administration of sulfanilamide and its allied compounds. On the basis of my experience, it appears that severe depression of the bone marrow is especially liable to follow the use of these drugs in cases in which infection has already damaged the leukopoietic tissue. In my first 2 cases it seemed reasonable to implicate the infectious process as the cause of the original depression of the bone marrow. Because of the chemotherapy received on admission, interpretation of the behavior of the white cell count in the third case was more difficult. It was my impression that the early decrease in the leukocyte count during chemotherapy was merely indicative of control of the acute part of the infection and that subsequent lowering was due to the persistence of a low grade infectious process. The secondary fall in the absolute number of polymorphonuclears in this case can be attributed to the continuance of the otitis and mastoiditis and also to the superimposed infection of the upper respiratory tract.

Fitz-Hugh and Krumbhaar [21] were among the first to give an adequate description of the changes in the bone marrow in neutropenic

21. Fitz-Hugh, T., Jr., and Krumbhaar, E. B.: Myeloid Cell Hyperplasia of Bone Marrow in Agranulocytic Angina, Am. J. M. Sc. **183**:104 (Jan.) 1932.

states. They described the marrow as being hyperplastic rather than hypoplastic, as was originally thought. In those patients who recovered, the marrow invariably showed the same two features, namely, an arrest of the maturation of the myeloid cells and a failure of delivery of these immature cells to the peripheral blood. The marrow of patients who died was also hyperplastic, but the normal myeloid cells were replaced in greater part by cells of the plasmocytic series. The changes in the marrow [22] found in my 3 cases correspond closely with those previously described as having occurred in cases in which the patients recovered. The usual picture of arrest of maturation with marked increase in the number of myelocytes and promyelocytes (the terminology is that of Osgood and Ashworth) [23] was seen. In addition, there was evidence of increased mitotic activity among the promyelocytes, and vacuoles and toxic granules were numerous. Serial aspirations of marrow showed progressive maturation coincident with improvement in the peripheral blood picture (tables 1, 2 and 3). Figures 4 and 5 illustrate the types of cells seen.

TABLE 1.—*Progressive Improvement of the Peripheral Blood Picture Associated with Maturation of the Bone Marrow in Patient M. G.*

Type of Cell	Dec. 15, 1939		Dec. 23, 1939		Jan. 4, 1940		Range in Normal Sternal Marrow, %
	Blood, %	Sternal Marrow, %	Blood, %	Sternal Marrow, %	Blood, %	Sternal Marrow, %	
Segmented neutrophils	4.0	0.0	28.0	1.0	41.0	18.0	9-30
Segmented eosinophils	4.0	0.0	0.0	1.0	0.0	0.0	0- 3
Segmented basophils	0.0	0.0	0.0	0.0	0.0	0.0	0- 0.5
Nonsegmented neutrophils	0.0	8.0	7.0	27.0	0.0	37.0	20-40
Nonsegmented eosinophils	0.0	0.0	0.0	1.5	0.0	0.5	0- 2
Nonsegmented basophils	0.0	0.0	0.0	0.0	0.0	0.0	0- 1
Neutrophilic metamyelocytes	0.0	5.0	0.0	7.5	0.0	2.0	3- 4
Eosinophilic metamyelocytes	0.0	0.0	0.0	0.0	0.0	0.0	0- 3
Neutrophilic myelocytes	0.0	40.0	0.0	25.0	0.0	5.5	3-12
Promyelocytes type 1	0.0	2.0	0.0	3.0	0.0	4.0	0.5- 5
Promyelocytes type 2	0.0	10.5	0.0	5.0	0.0	2.5	
Myeloblasts	0.0	8.0	0.0	8.5	0.0	3.0	0- 3
Lymphocytes	77.0	4.5	46.0	10.0	49.0	12.5	5-20
Monocytes	15.0	1.0	19.0	1.5	10.0	3.0	0- 5
Normoblasts	0.0	20.0	0.0	7.5	0.0	11.5	9-26
Megaloblasts	0.0	1.0	0.0	1.5	0.0	0.5	0- 4

22. Marrow was obtained by aspiration from the manubrial portion of the sternum, according to a method similar to that described by Young and Osgood (Sternal Marrow Aspirated During Life, Arch. Int. Med. **55**:186 [Feb.] 1935). The manubrium was found to be the most satisfactory area for aspiration, since in young infants there is almost invariably a center of ossification present in the middle portion of this bone. Blood smears were made simultaneously with the marrow smears, and differential counts of 200 cells were made.

23. Osgood, E. E., and Ashworth, C. M.: Atlas of Hematology, San Francisco, J. W. Stacey, Inc., 1937.

In order that a prognosis may be given, it is important to follow the bone marrow picture in cases of granulocytopenia, whether the depression is due to administration of sulfanilamide or its allied com-

TABLE 2.—*Progressive Improvement of the Peripheral Blood Picture Associated with Maturation of the Bone Marrow in Patient M. R.*

Type of Cell	Feb. 3, 1940		Feb. 17, 1940		Range in Normal
	Blood, %	Sternal Marrow, %	Blood, %	Sternal Marrow, %	Sternal Marrow, %
Segmented neutrophils	9.0	2.0	39.0	7.5	9-30
Segmented eosinophils	0.0	0.0	0.0	0.0	0- 3
Segmented basophils	0.0	0.0	0.0	0.0	0- 0.5
Nonsegmented neutrophils	46.0	11.5	14.0	32.5	20-40
Nonsegmented eosinophils	0.0	1.0	0.0	0.0	0- 2
Nonsegmented basophils	0.0	0.0	0.0	0.0	0- 1
Neutrophilic metamyelocytes	0.0	1.0	0.0	5.0	3- 4
Eosinophilic metamyelocytes	0.0	0.0	0.0	0.0	0- 3
Neutrophilic myelocytes	1.0	27.5	11.0	20.0	3-12
Promyelocytes type 1	0.0	26.5	0.0	5.0	0.5- 5
Promyelocytes type 2	0.0	2.0	0.0	0.5	
Myeloblasts	0.0	0.0	0.0	2.0	0- 3
Lymphocytes	20.0	13.5	19.0	15.0	5-20
Monocytes	24.0	0.0	17.0	0.0	0- 5
Normoblasts	0.0	14.0	0.0	11.5	9-26
Megaloblasts	0.0	1.0	0.0	1.0	0- 4

TABLE 3.—*Progressive Improvement of the Peripheral Blood Picture Associated with Maturation of the Bone Marrow in Patient W. B.*

Type of Cell	April 16, 1940		April 30, 1940		May 17, 1940		June 5, 1940		Range in Normal
	Blood, %	Sternal Marrow, %	Blood, %	Sternal Marrow, %	Blood, %	Sternal Marrow, %	Blood, %	Sternal Marrow, %	Sternal Marrow, %
Segmented neutrophils	11.0	0.0	68.0	7.5	22.0	0.0	50.0	10.0	9-30
Segmented eosinophils	3.0	1.5	1.0	4.0	6.0	0.0	0.0	3.0	0- 3
Segmented basophils	0.0	0.0	0.0	0.0	0.0	0.0	0.5	0.0	0- 0.5
Nonsegmented neutrophils	1.0	2.0	3.0	22.0	12.0	14.5	3.5	28.5	20-40
Nonsegmented eosinophils	0.0	7.5	1.0	3.5	0.0	1.0	0.0	3.5	0- 2
Nonsegmented basophils	0.0	0.5	0.0	0.0	0.0	0.0	0.0	0.0	0- 1
Neutrophilic metamyelocytes	0.0	0.5	0.0	5.5	0.0	0.0	0.0	2.0	3- 4
Eosinophilic metamyelocytes	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0- 3
Neutrophilic myelocytes	0.0	11.0	0.0	15.0	0.0	23.0	0.0	7.0	3-12
Promyelocytes type 1	0.0	7.0	0.0	6.0	0.0	14.0	0.0	5.0	0.5- 5
Promyelocytes type 2	0.0	28.5	0.0	8.0	0.0	15.0	0.0	1.0	
Myeloblasts	0.0	1.5	0.0	1.0	0.0	2.0	0.0	0.0	0- 3
Lymphocytes	24.5	5.5	6.0	5.5	18.0	13.0	40.0	21.0	5-20
Monocytes	60.5	1.0	21.0	1.0	42.0	1.0	6.0	1.5	0- 5
Normoblasts	0.0	29.5	0.0	20.0	0.0	16.0	0.0	16.5	9-26
Megaloblasts	0.0	4.0	0.0	1.0	0.0	0.0	0.0	1.0	0- 4

pounds or to some infectious process. Aspiration of sternal marrow is a simple, almost painless procedure that can be carried out in office practice. An appraisal of the types of cells based on a differential count of 200 cells is adequate for determination of the state of the bone marrow. Because of the possible admixture with blood during aspiration, quantitative studies are apt to be inaccurate.

During the past few years new claims have been made for the various agents of use in treatment of granulocytopenia. Jackson and Tighe [24] stated that the mortality in a large series of patients was reduced from 78 per cent among untreated patients to 35 per cent among those treated with pentnucleotide. More recently, value has

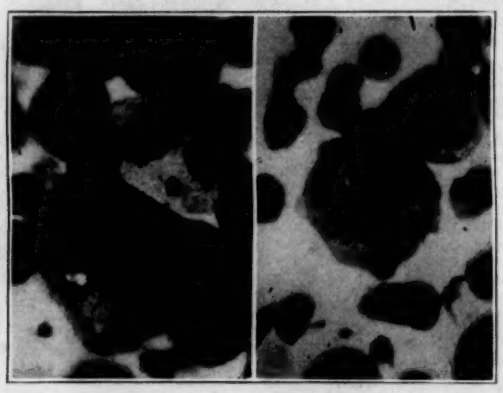

Fig. 4.—Promyelocytes in mitosis. Such division of cells is only occasionally seen in normal marrow but is frequently found in immature marrow.

Fig. 5.—Cells in bone marrow. *A*, three myelocytes and one promyelocyte, the types of cells which occur in large numbers in immature marrow. *B*, nonsegmented neutrophils, the type of cell which dominates the picture in mature marrow.

been attached to the intravenous injection of vitamin C. According to the observations of Kalk,[25] the number of granulocytes in the peripheral

24. Jackson, H., Jr., and Tighe, T. J. G.: Analysis of Treatment and Mortality of Three Hundred and Ninety Cases of Acute Agranulocytic Angina, New England J. Med. **220**:729 (May 4) 1939.

25. Kalk, H.: Agranulozytose und Vitamin C, Deutsche med. Wchnschr. **65**: 1624 (Nov. 3) 1939.

blood was increased and there was prompt clinical improvement after the intravenous injection of ascorbic acid. Marberg and Wiles [26] recommended the daily administration of fresh strained yellow bone marrow.

It is exceedingly difficult to evaluate the role of any form of therapy, since many patients with this disease recover spontaneously. All of my patients exhibited the type of bone marrow seen in cases in which the outcome is favorable and would probably have recovered without pentnucleotide therapy. In fairness to this form of treatment, it must be mentioned that all 3 patients showed a definite rise in the polymorphonuclear count, which previously had been falling or had been stationary at a low level. In the case of W. B., an opportunity presented itself to give pentnucleotide therapy during one period of granulocytopenia and to give no specific therapy during a subsequent period of leukopoietic depression. The difference in the response to these two forms of treatment is best appreciated by reference to figure 3. Although discontinuance of administration of the chemotherapeutic agent is probably the only measure necessary when the granulocytes reach a low level, pentnucleotide appears to accelerate the rate of recovery of the bone marrow, and this drug may prove to be a useful therapeutic addendum for us with young patients. A combination of attempts to control the infection, discontinuance of administration of drugs which may affect the bone marrow, use of frequent transfusions and administration of pentnucleotide seems the logical method of treatment.

SUMMARY

Three cases of granulocytopenia apparently due to infection are described. The effect of chemotherapy in these cases is discussed. It is suggested that particular care be taken in the administration of chemotherapeutic agents to infants whose bone marrow is already depressed by infection. In such patients small doses of the drug administered over a relatively short time may cause severe granulocytopenia. The belief is set forth that mere discontinuance of administration of the drug is probably adequate when the granulocytes reach an alarmingly low level but that pentnucleotide therapy accelerates the rate of recovery of the bone marrow. Results of comparative studies of the blood and bone marrow are tabulated.

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26. Marberg, C. M., and Wiles, H. O.: The Granulocytopoietic Fraction of Yellow Bone Marrow, Arch. Int. Med. **61**:408 (March) 1938.

ENLARGEMENT OF THE THYROID GLAND IN JUVENILE PATIENTS WITH DIABETES MELLITUS

INCIDENCE OF DIABETES AND THYROID DISEASE IN THE FAMILY

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The association of disease of the thyroid gland with juvenile diabetes mellitus is infrequently noted in the literature. Strouse [1] stated that disturbances of the ductless glands and diabetes in children are not often encountered together. John [2] collected 285 cases of hyperthyroidism in children and stated:

> On the whole, hyperthyroidism plays but an insignificant part as an etiologic factor in the production of diabetes in children. When abnormalities in the carbohydrate metabolism are found, they should be controlled thoroughly by a liberal diet and a sufficient amount of insulin to insure proper utilization of the food.

Greenwald and Collens [3] found only 5 cases of diabetes associated with hypothyroidism reported in the literature; they added a case of their own. Wagner [4] observed an obese 12 year old girl who had diabetes with definite hypothyroidism, which usually is accompanied by an increased tolerance for dextrose. Lindblom [5] studied the case of a 16 year old boy with hypothyroidism and severe diabetes who died in coma. Lusk [6] stated that myxedema might abolish diabetes, which, however, sometimes returned when the basal metabolic rate approached normal. In this connection, Wilder [7] cited the interesting case of a

From the Metabolic Clinic of the Children's Memorial Hospital.

1. Strouse, S., in Abt, I.: Pediatrics, Philadelphia, W. B. Saunders Company, 1923, vol. 2, p. 768.
2. John, H. J.: The Diabetic Child, Ann. Int. Med. **8**:198 (Aug.) 1934.
3. Greenwald, H. M., and Collens, W. S.: Hypothyroidism Complicated by Diabetes Mellitus, Am. J. Dis. Child. **50**:979 (Oct.) 1935.
4. Wagner, R.: Die Besonderheiten des kindlichen Diabetes, Wien. med. Wchnschr. **76**:986, 1926.
5. Lindblom, S.: Severe Case of Diabetes Mellitus with Multiple Endocrine Disturbances, Hygiea **78**:721, 1916.
6. Lusk, G.: The Elements of the Science of Nutrition, ed. 4, Philadelphia, W. B. Saunders Company, 1928.
7. Wilder, R. M.: Hyperthyroidism, Myxedema and Diabetes, Arch. Int. Med. **38**:736 (Dec.) 1926.

juvenile patient with myxedema who had symptoms of diabetes when the basal metabolic rate was increased from — 45 to — 10 per cent by the administration of thyroid.

We have observed that the association of hyperthyroidism with juvenile diabetes mellitus brings about a striking change in the diabetic state, as illustrated in the following 2 cases.

TWO CASES OF JUVENILE DIABETES MELLITUS ASSOCIATED WITH HYPERTHYROIDISM

CASE 1.—E. L., a 9 year old white girl, was brought to the Children's Memorial Hospital because of increased appetite, polyuria, nocturia, increased thirst and loss of weight for the past three weeks. There was no history of diabetes in the family. The mother had had a goiter removed about twelve years before and appeared in good health.

On examination, the patient appeared thin and poorly nourished. The thyroid gland was not palpable. The pulse rate was 108 per minute, and there was a

TABLE 1.—*Clinical Data for Case 1*

Date	Weight, Pounds	Diet, Calories	Insulin, Units	Pulse Rate per Minute	Basal Metabolic Rate, per Cent
11/23/31	48½	1,824	16	...	+8
1/11/32	56	.....	16	...	.....
7/11/32	57¾	.....	12	...	.....
12/ 5/32	59¼	.....	16	...	.....
3/ 6/33	61¾	2,042	20	...	.....
7/24/33	69¼	.....	44	112	.....
12/11/33	73	.....	42	...	.....
2/ 5/34	75	2,150	44	...	+19, +26
8/18/34	78	.....	52	130	+35, +48
11/19/34	82½	.....	58	100	.....
2/18/35	85½	.....	58	100	+31, +40
7/22/35	90	2,294	66	114	.....

systolic murmur over the precordium. The fasting blood sugar was 154 mg. per hundred cubic centimeters, and examinations of the urine gave positive results for sugar, acetone and diacetic acid. After regulation of her regimen in the hospital, the patient was discharged, with instructions to limit her diet to 1,825 calories and to take 8 units of regular insulin before breakfast and 10 units before supper (table 1).

In December 1931 the basal metabolic rate was + 8 per cent. At this time compound solution of iodine U. S. P. was added to the diet. Toward the end of the year the urine frequently contained sugar and the patient's condition became hard to manage. The dosage of insulin was gradually increased to 14 units before breakfast and 12 units before supper. However, despite an increase in the diet, the gain in weight was not satisfactory. In June 1933 the thyroid gland became prominent and the pulse rate averaged 120 per minute. There was frequent glycosuria. The dosage of insulin was 20 units before breakfast and 20 units before supper. In March 1934 values for the basal metabolic rate were + 19 and + 26 per cent. Six months later they had increased to + 35 and + 48 per cent. The thyroid gland remained enlarged, and there was no bruit. Glycosuria was often observed, and the dose of insulin was again increased. The pulse rate was 114 per minute, and the blood pressure was 116 systolic and 70 diastolic. The gain in weight at this time was satisfactory.

The patient has been seen at irregular intervals by one of us (A. L. N.) since her discharge from the outpatient department. The thyroid gland has remained enlarged, and the pulse rate is above normal. There is frequent glycosuria.

CASE 2.—K. K., an 8 year old white girl, was brought to the Children's Memorial Hospital because of polyuria and loss of weight for the past two months. There was no history of diabetes in the family. The mother had undergone thyroidectomy because of exophthalmic goiter and appeared in good health.

On examination, the patient was thin and poorly nourished. The thyroid gland was not palpable. The fasting blood sugar was 240 mg. per hundred cubic centimeters, and examinations of the urine gave positive results for sugar, acetone and diacetic acid. After regulation of her regimen in the hospital, the patient was discharged, with instructions to limit her diet to 1,700 calories and to take 12 units of regular insulin before breakfast and 8 units before supper (table 2).

TABLE 2.—*Clinical Data for Case 2*

Date	Weight, Pounds	Diet, Calories	Insulin,* Units	Pulse Rate per Minute	Basal Metabolic Rate, per Cent
4/21/32	48	1,404	R 20	...	.....
12/12/32	60½	1,848	R 9	...	.....
3/13/33	60	1,921	R 9	...	.....
9/25/33	63½	1,978	R 7	...	.....
1/22/34	66¾	.....	R 11	...	.....
6/25/34	66	.....	R 8	...	.....
12/10/34	75½	.....	R 30	...	+8, +15
6/ 3/35	76¾	.....	R 44	...	.....
11/25/35	84	2,278	R 44	...	.....
6/ 8/36	90¾	.....	R 30	...	.....
12/ 4/36	91½	.....	P 36, R 8	...	.....
1/22/37	95¼	.....	P 40, R 30	106	.....
6/13/37	96½	.....	P 48, R 6	...	+22
9/ 3/37	100¾	.....	P 44, R 81	...	+35
10/ 2/37	101¾	.....	P 96, R 40		
1/12/38	104¼	.....	P 64, R 34		
5/25/38	104	.....	P 72, R 34		
12/ 3/38	107¾	.....	P 80, R 16		
6/10/39	103	.....	P 80, R 16		
9/ 8/39	100¾	.....	P 80, R 16		
12/10/39	107¼	.....	P 20, R 18		
2/ 4/40	105	.....	P 24, R 30		
6/13/40	108¼	.....	P 24, R 36		

* R signifies amorphous insulin; P, protamine zinc insulin.

In October 1934 intermittent glycosuria was discovered and the patient's condition became hard to manage. Compound solution of iodine U. S. P. was added to the diet, and the dosage of insulin was increased to 20 units before breakfast, 6 units before lunch and 10 units before supper. In January 1935 determinations of the basal metabolic rate gave + 8 and + 15 per cent. Subsequently, the dosage of insulin was increased to 40 units before breakfast, 16 units before lunch and 12 units before supper. In January 1937 the pulse rate averaged 106 per minute, and there was a systolic murmur over the precordium. In July 1937 the basal metabolic rate was + 35 per cent, and the dosage of insulin was 40 units of protamine zinc insulin before breakfast, with 20 to 30 units of regular insulin. The following month there was almost constant glycosuria. In September 1937 administration of 50 units of protamine zinc insulin and between 25 and 40 units of regular insulin became necessary to control the glycosuria. Two years later the patient required 134 units of insulin daily. In February 1940 the patient had chronic bronchitis and required 36 units of protamine zinc insulin and 36 units of regular insulin before breakfast and 16 units of regular insulin before supper. In June 1940 the patient was somewhat improved and had gained about 3 pounds (1.3 Kg.) since the beginning of the year.

The foregoing 2 cases have several features in common, including an almost identical course of the disease. The onset of diabetes occurred at about the same age, the thyroid gland became palpable early in the course and both patients had mothers who had been subjected to thyroidectomy. Both patients showed rather persistent glycosuria despite "adequate" insulin and a controlled diet and as the disease progressed the requirement of insulin steadily increased, so that 1 patient was given 134 units daily. These developments suggested either an underlying complication or an additional metabolic or endocrine disturbance, and determination of the basal metabolic rate gave values of + 48 per cent in 1 case and +35 per cent in the other. Surgical intervention could not be resorted to in either of these cases.

INVESTIGATION ON THE RELATION OF A PALPABLE THYROID IN JUVENILE PATIENTS WITH DIABETES TO FAMILY INCIDENCE OF DIABETES AND THYROID DISEASE

The course of the disease in the foregoing 2 cases prompted us to investigate the occurrence of a palpable thyroid gland in our juvenile diabetic patients [8] and the incidence of diabetes and thyroid disease in the families of these subjects. White [9] noted the occurrence of a palpable thyroid gland in 6 per cent of her cases and found a history of thyroid disease in the family in 3.6 per cent. Brown and Thompson,[10] in reporting the results of their investigation, stated: "The only other physical abnormality reported in the families of our diabetic subjects to a greater extent than in the general population is a disturbance in the functioning of the thyroid gland."

We have summarized the result of our investigation in tables 3 to 6. Of 128 juvenile diabetic patients seen in the clinic of the Children's Memorial Hospital, 26 (20 per cent) had a definitely palpable thyroid gland and 102 (80 per cent) a normal thyroid gland. In the group with a palpable thyroid gland there were 14 boys and 12 girls. The ages in this group varied from 5 to 16 years, 15 (57 per cent) of the children being between 8 and 12 years of age. The onset of diabetes occurred between the ages of 4 and 10 years in 23 (88 per cent) of these patients with a palpable thyroid.

Of the 128 diabetic subjects 33 (25 per cent) had a history of diabetes in the family and 34 (27 per cent) a history of thyroid disease in the family. The difference between the incidence of diabetes and

8. The status of the thyroid gland was checked by several observers independently, both in the clinic of the outpatient department and in the hospital.

9. White, P.: Diabetes in Childhood and Adolescence, Philadelphia, Lea & Febiger, 1932.

10. Brown, G. D., and Thompson, W. H.: The Diabetic Child, Am. J. Dis. Child. **59**:238 (Feb.) 1940.

thyroid disease in the families of those subjects with and of those without a palpable thyroid gland is striking. Fifty per cent (13) of the subjects with a palpable thyroid gland had a family history of diabetes as compared with 19 per cent (20) of those with a normal thyroid gland. The incidence of thyroid disease in the family is even more remarkable. Eighty per cent (21) of those subjects with a palpable thyroid gland had families in which there was a history of thyroid disease, as compared with 12 per cent (13) of those with a normal thyroid gland.

TABLE 3.—*Distribution by Age and Sex of Juvenile Patients with Diabetes Who Had a Palpable Thyroid Gland*

Age Group	Boys	Girls	Total
5 yr. to 5 yr. 11 mo.	..	1	1
6 yr. to 6 yr. 11 mo.	..	1	1
7 yr. to 7 yr. 11 mo.	1	..	1
8 yr. to 8 yr. 11 mo.	1	..	1
9 yr. to 9 yr. 11 mo.	3	1	4
10 yr. to 10 yr. 11 mo.	2	3	5
11 yr. to 11 yr. 11 mo.	3	2	5
12 yr. to 12 yr. 11 mo.	1	1	2
13 yr. to 13 yr. 11 mo.	1	1	2
14 yr. to 14 yr. 11 mo.	1	..	1
15 yr. to 15 yr. 11 mo.	..	1	1
16 yr. to 16 yr. 11 mo.	1	1	2
Total	14	12	26

TABLE 4.—*Age at Onset of Diabetes of Juvenile Patients with Diabetes Who Had a Palpable Thyroid Gland*

Age at Onset	
4 yr. to 4 yr. 11 mo.	2
5 yr. to 5 yr. 11 mo.	2
6 yr. to 6 yr. 11 mo.	3
7 yr. to 7 yr. 11 mo.	3
8 yr. to 8 yr. 11 mo.	0
9 yr. to 9 yr. 11 mo.	7
10 yr. to 10 yr. 11 mo.	1
11 yr. to 11 yr. 11 mo.	1
12 yr. to 12 yr. 11 mo.	0
13 yr. to 13 yr. 11 mo.	0
14 yr. to 14 yr. 11 mo.	0
15 yr. to 15 yr. 11 mo.	1
Total	26

Table 6 shows that in 56 per cent (19) of the 34 families with thyroid disease there were also cases of diabetes. Sixty-eight per cent (13) of 19 were families of juvenile diabetic subjects with palpable thyroid glands, and 32 per cent (6) were families of subjects who had normal thyroid glands. Thyroidectomy had been performed in 12 instances; on 4 mothers, 2 fathers, 2 uncles and 6 aunts. It is of interest to find that in 2 of the 3 children born to a father who had undergone thyroidectomy and a mother with definite goiter and exophthalmos diabetes developed at the ages of 10 and 14 years, respectively. There were no other diabetic subjects in this family. In each

of 3 other families diabetes developed in 2 brothers between the ages of 10 and 13 years, respectively; the mothers in 2 of these 3 families had large adenomatous goiters, and the mother in 1 had an exophthalmic goiter. In 2 families other siblings showed evidence of thyroid disturbances: In 1 family 2 brothers and in the other (family of the patient in case 3) the older sister had goiters.

It has been suggested that hyperthyroidism may be one of the factors predisposing to the development of diabetes. Yet the part played by enlargement of the thyroid in the juvenile diabetic subject and the association with diabetes and with thyroid disease in the family have not received sufficient attention. A fairly large group of our series

TABLE 5.—*Incidence of Diabetes and of Thyroid Diseases in Families of Juvenile Patients with Diabetes*

	Total		With Diabetes in Family		With Thyroid Disease in Family	
	Number	Percentage	Number	Percentage	Number	Percentage
Patients with palpable thyroid	26	20	13	50	21	80
Patients with normal thyroid	102	80	20	19	13	12
Total	128		33	25	34	27

TABLE 6.—*Incidence of Diabetes Associated with Thyroid Diseases in Families of Juvenile Patients with Diabetes*

Patients with cases of	With Palpable Thyroid	With Normal Thyroid	Total
Thyroid disease in family	21	13	34
Diabetes in family	13	20	33
Diabetes associated with thyroid disease in family	13 (68%)	6 (32%)	19

of juvenile diabetic subjects in whom a palpable thyroid gland developed came from families in which instances of diabetes and thyroid disease were more frequent than in the families of "normal" diabetic subjects. Unless hyperthyroidism ensues, the enlargement of the thyroid does not appear to influence either the onset or the course of the diabetic condition.

While the interrelation of all the so-called glands of internal secretion in influencing the metabolic processes of the body is becoming more apparent, especially in carbohydrate metabolism,[11] it is of value to review some of the work on the relation of the action of the thyroid

11. John, H. J.: The Inter-Relationship of the Pancreas with Other Endocrine Glands in Diabetes, Am. J. Digest. Dis. & Nutrition **4**:4 (March) 1937. Marine, D.: Physiology and Principal Inter-Relations of the Thyroid Gland, Bull. New York Acad. Med. **15**:790 (Dec.) 1939.

gland to sugar metabolism. In 1867 Dumontpallier [12] called attention to the association of exophthalmic goiter and diabetes mellitus in some patients. Later, Brunton,[13] Hartman [14] and Budde [15] reported such cases in Europe, and in 1899 Manges [16] reported the first case in America. Since then the association of these two diseases has received considerable attention.[17]

Glycosuria has been known to occur in cases of hyperthyroidism, and when this symptom has been associated with hyperglycemia it has at times been difficult to determine whether it was related to the hyperthyroidism or indicated the presence of true diabetes mellitus. John [18] collected cases of hyperthyroidism from the literature and reported that the incidence of glycosuria varied greatly; it was present in 19 per cent of his own cases. Recently Andersen,[19] by a special technic, was able to demonstrate the presence of spontaneous glycosuria in 100 per cent of his 25 cases of hyperthyroidism. In all of these cases he was able to show that after the ingestion of 70 Gm. of dextrose determinations of blood sugar levels at ten minute intervals gave a higher and more protracted curve than normal. This subject was reviewed by Fitz [20] in 1921 and later, in a detailed monograph, by Andersen.[21]

The cause of glycosuria in cases of hyperthyroidism and its relation to the development of true diabetes have been the subject of numerous investigations. More recently, another approach to an understanding

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12. Dumontpallier: Goître exophtalmique et glycosurie chez la même malade, Compt. rend. Soc. de biol. **19**:116, 1867.

13. Brunton, T. L.: Cases of Exophthalmic Goitre, St. Barth. Hosp. Rep. **10**: 255, 1874.

14. Hartman, W. C.: Ueber zwei mit Basedow'scher Krankheit complicerte Fälle von Diabetes mellitus, Inaug. Dissert., Tubingen, L. F. Fues, 1878, pp. 24-80.

15. Budde, V.: Basedow's Disease Complicated by Diabetes Mellitus, Ugesk. f. læger **22**:49, 1890; abstracted, Neurol. Centralbl. **10**:112, 1891; cited by Fitz.[20]

16. Manges, M.: A Case of Exophthalmic Goiter with Diabetes Mellitus and Pigmentation, Mt. Sinai Hosp. Rep. **2**:59, 1899.

17. John, H. J.: Carbohydrate Metabolism in Hyperthyroidism, Endocrinology **11**:497 (Nov.-Dec.) 1927. Joslin, E. P., and Lahey, F. H.: Diabetes and Hyperthyroidism, Am. J. M. Sc. **176**:1 (July) 1928; Diabetes and Hyperthyroidism, Ann. Surg. **100**:629 (Oct.) 1934. Wilder, R. M.: Hyperthyroidism, Myxedema and Diabetes, Tr. A. Am. Physicians **41**:113, 1926. Joslin, E. P.: Treatment of Diabetes, Philadelphia, Lea & Febiger, 1937, p. 569.

18. John, H. J.: Hyperthyroidism Showing Carbohydrate Metabolism Disturbances, J. A. M. A. **99**:620 (Aug. 20) 1932.

19. Andersen, W. T.: An Occurrence of Spontaneous Glycosuria and Alimentary Hyperglycemia in Exophthalmic Goiter, Acta med. Scandinav. **78**:229, 1932.

20. Fitz, R.: Relation of Hyperthyroidism to Diabetes Mellitus, Arch. Int. Med. **27**:305 (March) 1921.

21. Andersen, W. T.: Studies in Blood Sugar and Glycosuria in Exophthalmic Goiter, Copenhagen, Levin & Munksgaard, 1933.

of the mechanism of hyperglycemia in cases of hyperthyroidism has been demonstrated by Althausen.[22] He showed that the administration of thyroxin to rats accelerates the absorption of utilizable sugars from the intestine. Conversely, thyroidectomy slows the absorption of dextrose from the intestine. By means of a "galactose test" he observed that the average galactose tolerance curve in cases of hyperthyroidism was more than three times as high as the average tolerance curve for this sugar for normal controls and for patients with diseases other than hyperthyroidism.[23] This phenomenon he attributed to the accelerating effect of the thyroid hormone in cases of hyperthyroidism; after thyroidectomy the galactose tolerance curve approached normal.

On the basis of an abnormally rapid absorption of sugars from the intestine, combined with an increased utilization of dextrose by the tissues,[24] other peculiarities of carbohydrate metabolism in cases of hyperthyroidism have been explained. The increased absorption of carbohydrate accounts for the "diabetic" manifestations of glycosuria, postprandial hyperglycemia and high dextrose tolerance curves. Moreover, the increased utilization of carbohydrate accounts for the normal or greater than normal arteriovenous blood sugar difference,[25] the postprandial rise in the respiratory quotient[26] and the fall in the level of inorganic phosphates in the blood.[27] The chronic depletion of glycogen reserves, which explains the low fasting respiratory quotient, leads to a compensatory acceleration of fat catabolism which, as in the case of "hunger diabetes," results in the incomplete oxidation of fatty acids and brings about acidosis.

Since the derangement of carbohydrate metabolism in cases of hyperthyroidism often simulates that in cases of true diabetes and since hyperthyroidism may be one of the factors which precipitate the development of diabetes, especially in subjects who have the diabetic "tendency," it is essential to observe such patients carefully before and after thyroidectomy to avoid making an erroneous diagnosis of diabetes or overlooking true diabetes as a complicating factor. For this reason,

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22. Althausen, T. L.: Disturbance of Carbohydrate Metabolism in Hyperthyroidism, J. A. M. A. **115**:101 (July 13) 1940.

23. Althausen, T. L.; Lockhart, J. C., and Soley, M. H.: A New Diagnostic Test (Galactose) for Thyroid Disease, Am. J. M. Sc. **199**:342 (March) 1940.

24. Mirsky, I. A., and Boh-Kahn, R. H.: Effect of Experimental Hyperthyroidism on Carbohydrate Metabolism, Am. J. Physiol. **117**:6 (Sept.) 1936.

25. Trumper, M., and Cantarow, A.: Biochemistry in Internal Medicine, Philadelphia, W. B. Saunders Company, 1932, p. 45.

26. Sanger, B. J., and Hun, E. G.: Glucose Mobilization Rate in Hyperthyroidism, Arch. Int. Med. **30**:397 (Sept.) 1922.

27. Katayama, I.: Significance of Changes in the Composition of Blood and Urine After Ingestion of Glucose, J. Lab. & Clin. Med. **11**:1024 (Aug.) 1926.

we are reporting the case of a girl with hyperthyroidism, who had a family history of diabetes and who showed glycosuria, hyperglycemia and impaired tolerance for dextrose and galactose.

A CASE OF HYPERTHYROIDISM IN WHICH THERE WERE SYMPTOMS OF DIABETES

CASE 3.—E. R., a 10 year old white girl, was admitted to the Children's Memorial Hospital on March 17, 1938 because of nervousness, excitability and increased appetite for the past three months. Her younger sister had diabetes;

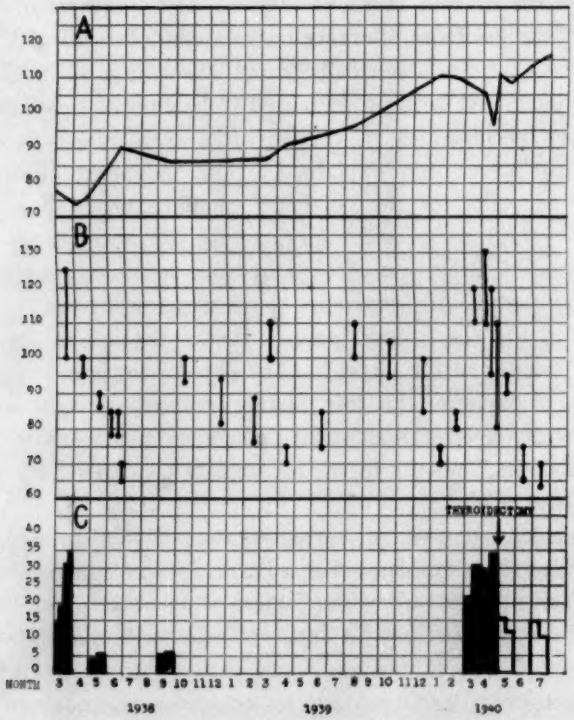

Chart 1 (case 3).—Course of the illness. *A*, weight (in pounds); *B*, pulse rate per minute, and *C*, basal metabolic rate. In *C*, solid areas indicate a plus and white areas a minus value.

there was no other history of diabetes or of thyroid disease in the family. On examination, she appeared well nourished and weighed 77¼ pounds (35 Kg.). Her eyelids fluttered constantly, and there was slight exophthalmos. The thyroid gland was enlarged and smooth; no bruit was heard. The lungs were clear and the heart was normal. The blood pressure was 136 systolic and 60 diastolic. The pulse rate was 124 per minute. The skin was warm and moist, and there was a fine tremor of the outstretched hands. The clinical impression was hyperthyroidism (fig. 1).

During her stay in the hospital, the pulse rate varied from 100 to 125 per minute despite bed rest and sedatives. Examination of the urine gave negative

results for sugar. The values for the basal metabolic rate were + 14.9 and + 19.3 per cent. About one week later they had increased to + 32.5 and + 35 per cent. Subsequently, she improved clinically and was discharged from the hospital on April 14, weighing 74¼ pounds (33.7 Kg.).

One week later the patient was seen in the outpatient department. She weighed 76¾ pounds (34.8 Kg.) and appeared less nervous. The pulse rate was 96 per minute. Subsequently, she continued to gain weight, and the values for the basal metabolic rate dropped to + 3 and + 5.8 per cent. The pulse rate varied from 78 to 88 per minute. On Sept. 9, 1939 she complained of palpitation over the precordium. A bruit was heard over the thyroid gland. She remained under close

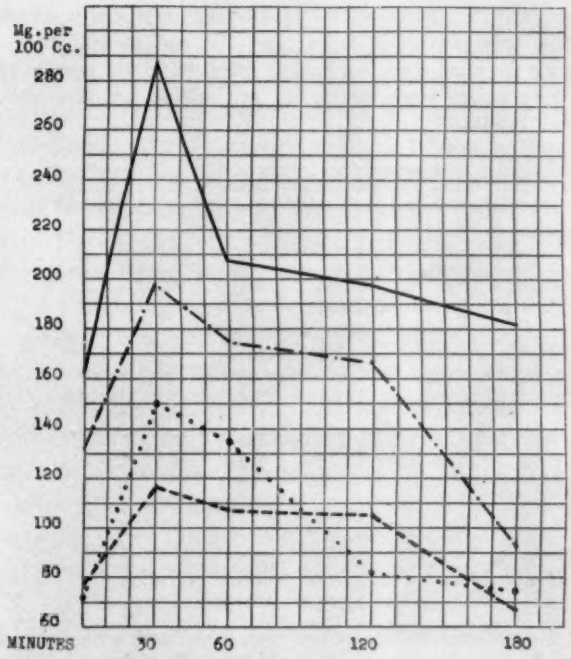

Chart 2 (case 3).—Dextrose tolerance curves before hospitalization (solid line), after institution of high carbohydrate diet and daily administrations of compound solution of iodine U. S. P. (line of dots and dashes and broken line) and ten weeks after thyroidectomy (dotted line).

observation and progressed fairly well at home. On Feb. 19, 1940 the median lobe of the thyroid gland was observed to be definitely enlarged; the pulse rate varied between 86 and 90 per minute; the weight was 110¼ pounds (50 Kg.). About one month later a definite change in the clinical course of this patient was observed. There developed marked tremor of the hands, nervousness and jerky movements of the body. The pulse rate varied between 110 and 120 per minute, and the basal metabolic rate had increased to + 23.6 and + 31.2 per cent; a dextrose tolerance test showed impaired tolerance, with a fasting blood sugar of 161 mg. per hundred cubic centimeters (fig. 2). Despite increased rest and a more liberal diet at home the patient continued to lose weight, so that by April 1940 she had lost 4 pounds (1.8 Kg.) in two months. At this time, also, the

right lobe of the thyroid gland was larger than the left. Two weeks later she had lost another pound (0.5 Kg.) and complained of nervousness and headache. For the first time glycosuria was discovered.

It was thought advisable to hospitalize the patient, in preparation for thyroidectomy. She was put to bed and given a high carbohydrate diet, with 10 minims (0.61 cc.) of compound solution of iodine U. S. P. and 10 grains (0.65 Gm.) of sodium bromide three times daily. She weighed 99 pounds (44.9 Kg.). During the first week of hospitalization the pulse rate varied from 100 to 130 per minute. A galactose tolerance test [28] showed an increased amount of the sugar in the blood after thirty minutes (fig. 3). The serum cholesterol was 136 mg. per hundred cubic centimeters of blood. Another dextrose tolerance test showed marked improvement. During the second week in the hospital the patient appeared less nervous; the pulse rate was lower, and she had gained about 3 pounds (1.3 Kg.). During the third week her weight increased to 110 pounds (49.9 Kg.), and the pulse rate varied from 80 to 110 per minute. A galactose tolerance test gave normal results.

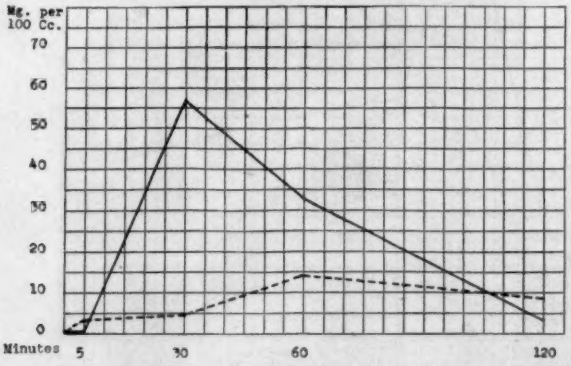

Chart 3 (case 3).—Galactose tolerance curves before (solid line) and after (broken line) administration of compound solution of iodine U. S. P. was begun.

On May 11, 1940 subtotal thyroidectomy was preformed, with the patient under anesthesia induced with nitrogen monoxide and oxygen. The postoperative condition was good, and there was a moderate reaction; the pulse rate rose to 132 per minute and the temperature reached 102 F. Intravenous instillation of 5 per cent solution of dextrose with 1 Gm. of sodium iodide was given. The temperature and the pulse rate became normal on the third postoperative day. The administration of 10 minims (0.61 cc.) of compound solution of iodine U. S. P. three times daily was continued. On May 21 the patient was discharged from the hospital and weighed 108 pounds (49 Kg.).

The pathologic diagnosis based on the excised thyroid gland was "diffuse goiter, with hyperplasia and changes consistent with iodine treatment."

About one week after discharge from the hospital the patient appeared normal and weighed 110¾ pounds (50.2 Kg.). She was given 5 minims (0.31 cc.) of

28. Forty grams of galactose dissolved in about 400 cc. of water and flavored with lemon juice was given by mouth after the patient had fasted overnight. Specimens of blood were obtained from the cubital vein before and five, thirty, sixty and one hundred and twenty minutes after administration of the galactose.

compound solution of iodine U. S. P. daily. Six weeks after thyroidectomy the basal metabolic rate was —11 per cent. The result of a dextrose tolerance test was normal, and there was no glycosuria or hyperglycemia. The patient showed no irritability at home and had no complaints. There was no tremor of the hands, and the heart was normal.

COMMENT

The effect of hyperthyroidism on carbohydrate metabolism is well illustrated in case 3. Because of the family history of diabetes, one might logically suspect that these changes were the result of a diabetic "tendency" or of latent diabetes activated by the hyperthyroidism. One cannot deny that this may occur, yet careful study and prolonged follow-up of such cases are necessary before one can make a definite diagnosis. It was interesting to observe the improvement in dextrose tolerance after the patient was made to rest and given a high calory diet and compound solution of iodine U. S. P. was administered. This improvement would not have occurred without the use of insulin if diabetes had been a complicating factor. In the galactose tolerance test carried out before the preoperative treatment was instituted,[23] the blood sugar level was 56 mg. per hundred cubic centimeters thirty minutes after the giving of galactose, and the results of the test were normal after a regimen of rest and administration of compound solution of iodine U. S. P. was instituted. We believe that although diabetes mellitus may eventually develop in this patient because of the familial tendency, the elimination of the hyperthyroidism may lessen the chance of development of juvenile diabetes.

The differentiation of diabetes and hyperthyroidism is sometimes difficult and the latter disease is often overlooked. Thus, Holst [29] cautioned that every diabetic subject should have a basal metabolism test and every hyperthyroid subject a sugar analysis. There is a great similarity in if not an actual identity of the cardinal symptoms of the two diseases. Polyphagia, polydypsia and loss of weight and strength are common to both. Sugar is frequently found in the urine of patients with hyperthyroidism, and hyperglycemia is fairly common. However, the mechanisms of glycosuria and hyperglycemia are different in the two diseases.

Patients with hyperthyroidism have glycosuria, postprandial hyperglycemia, impaired dextrose tolerance, a low respiratory quotient in the fasting state and depletion of the glycogen of the liver, which suggest the presence of diabetes mellitus; yet there are other physiologic findings which aid in the differentiation of this condition from diabetes mellitus. The utilization of sugar by the tissues is increased; the arteriovenous blood sugar difference is normal or increased in spite of an increased rate of blood flow; after a carbohydrate meal the rise in

29. Holst, J.: Glycosuria and Diabetes in Exophthalmic Goiter, Acta med. Scandinav. **55**:302, 1921.

the respiratory quotient is higher and the fall more rapid than normal, and the fall in the level of inorganic phosphates of the blood is normal; this fall is caused by the formation of a hexose phosphate compound in the process of utilization of dextrose by the tissues.

On the other hand, in diabetes mellitus there is a reduced capacity to utilize sugar, and the arteriovenous blood sugar difference is less than normal. Hence, less sugar is taken up by the tissues. After a carbohydrate meal the respiratory quotient remains low, and the fall in the level of inorganic phosphates of the blood following an increased supply of carbohydrate is less than normal.

When the two diseases coexist, the diagnosis of diabetes mellitus is usually made first. Certain features during the course of the illness, such as those in cases 1 and 2, should arouse suspicion that disease of the thyroid gland may be a complicating factor. Inability to control the glycosuria and the hyperglycemia with regulation of the diet and what seems to be an adequate dosage of insulin and failure of the patient to maintain weight or to gain weight are significant findings. Acidosis is prone to develop in these patients, especially if they are losing weight or are undernourished. Rapid pulse, restlessness, flushing, moist skin and tremor of the hands all aid in making the diagnosis of hyperthyroidism, particularly in younger patients.

SUMMARY AND CONCLUSIONS

The association of hyperthyroidism and diabetes mellitus appears to produce a change in the diabetic state, which in the first 2 cases reported in this paper was characterized by persistent glycosuria, failure of the patient to do well with a controlled diet and an "adequate" dosage of insulin and progressive increase in the daily requirement of insulin. The basal metabolic rates of the patients with diabetes in these 2 cases were + 35 and + 48 per cent, respectively.

The occurrence of a palpable thyroid gland in our juvenile diabetic subjects and its relation to the occurrence of diabetes and thyroid disease in the family have been investigated. Twenty per cent of the 128 subjects had a definitely palpable thyroid gland, and of these 50 per cent had a history of diabetes and 80 per cent a history of thyroid disease in the family, as compared with 19 and 12 per cent respectively of those subjects with a normal thyroid gland.

The disturbance of carbohydrate metabolism in cases of hyperthyroidism may simulate that in cases of diabetes mellitus, and careful study is necessary to avoid making an erroneous diagnosis or overlooking diabetes as a complicating factor.

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DEVELOPMENT OF THE CENTER FOR THE CUBOID BONE IN NEWBORN INFANTS

A ROENTGENOGRAPHIC STUDY

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A roentgenographic study of the osseous development of newborn white and Negro infants, measured in terms of the presence or absence of the center of ossification for the cuboid bone,[1] has been made in order to investigate the association between osseous development and (1) certain other criteria of maturity, namely, birth weight, crown-heel length at birth and gestational age and (2) certain maternal characteristics, namely, parity and age.

As has been pointed out, the conclusions are based on the presence or absence of the center of ossification for the cuboid bone in newborn infants. The study thus classifies the infants, according to their osseous development, into two sharply defined groups: (1) those in whom the center was present at the time a roentgenogram was made and (2) those in whom the center was not present at that time. It is obvious that study of the presence or absence of a center at a stated time fails to furnish data with regard to the time when the center appears. If it was present when the roentgenogram was made there is no information as to when it appeared; if it was absent there is no information as to when it will appear. For a group of infants in whom the center has been found to be present, data with regard to the size of the center would,

From the Division of Research in Child Development and the Division of Statistical Research of the Children's Bureau, United States Department of Labor.

1. A subsequent report will present the findings with regard to the presence or absence of each of nine other centers of ossification, namely, the calcaneus, the talus, the third cuneiform bone, the distal epiphysis of the femur, the proximal epiphysis of the tibia, the capitate bone, the hamate bone, the head of the humerus and the head of the femur.

of course, permit further differentiation—between infants in whom the center is large and those in whom it is of average size or small. Accurate measurement of the size of the center in large groups of infants is not practical, however, because with the technics available for mass studies the error of measurement is relatively large compared with the physiologic variation that exists in the size of the center, and the error may even conceal this variation. Of necessity, therefore, a presence or absence classification only was used in this study.

MATERIAL OF STUDY

Observations were made on 1,107 newborn infants (297 white boys, 266 white girls, 268 Negro boys and 276 Negro girls) born alive to women admitted to the obstetric wards of the Johns Hopkins Hospital from May 1936 to June 1937 and from May to December 1938. All the infants were single born, nonsyphilitic and in good enough physical condition to warrant subjection to roentgenographic examination within seventy-two hours of birth; they comprised more than half the single-born, nonsyphilitic infants born in the wards during the periods mentioned.

It should be pointed out that the mothers of these infants were a selected group in two ways: (1) in terms of socioeconomic status, for all were women admitted to the ward service of the hospital (infants born to mothers under the care of private physicians were excluded from the study); (2) obstetrically, for although all primiparas who applied were admitted to the hospital wards, as a rule a multipara was admitted only if she had a complication of pregnancy or some other condition that made her a "poor obstetric risk." The selection of these women in terms of their socioeconomic as well as their obstetric status limits the generalizations that can be made from the observations on the infants included in this study.

The steps taken in obtaining the data were as follows:

1. Each infant was weighed on admission to the nursery within twelve hours of birth.

2. The crown-heel length was measured within seventy-two hours of birth, with a Martin anthropometer.[2]

3. Roentgenograms were made within seventy-two hours of birth.

4. Each film was then read for the presence or absence of the center of ossification for the cuboid bone.

2. The following technic was used: The infant was placed on his back with the top of his head resting against the fixed upright of the anthropometer; the assistant held the head and shoulders of the infant in place; the measurer straightened the knees and held the feet together. Then the movable upright of the instrument was brought up firmly against the infant's soles, and the crown-heel length was read in centimeters and completed tenths of a centimeter.

5. The roentgenographic observations on each infant were recorded on a schedule, with the infant's race, sex, birth weight, crown-heel length at birth and gestational age and the mother's parity, age and complications of pregnancy.

METHOD OF ANALYSIS

Preliminary study of the roentgenograms of nearly half (498) of the infants examined in the course of this investigation showed that the development of the center for the cuboid bone in these infants varied with both race and sex.[3] These observations are confirmed by those reported in the present paper (based on a total of 1,107 infants): The center was present more frequently in Negro than in white infants of the same sex, and, within each racial group, it was present more frequently in girls than in boys.

Because the preliminary study showed such a marked association between skeletal maturity and both race and sex, the data in the present paper have been analyzed separately for white boys, white girls, Negro boys and Negro girls.

The data with regard to the presence of the center for the cuboid bone have been analyzed in relation to each of three criteria of the maturity of infants—birth weight, crown-heel length at birth and gestational age. Three groupings have been used for each criterion, as follows:

Birth weight:	Less than 2,500 Gm., 2,500 to 3,499 Gm. and 3,500 Gm. or more
Crown-heel length at birth:	Less than 47.0 cm., 47.0 to 49.9 cm. and 50.0 cm. or more
Gestational age:	Less than 38 weeks, 38 to 41 weeks and 42 weeks or more

These groupings have clinical as well as research significance, for a birth weight of less than 2,500 Gm., a crown-heel length at birth of less than 47 cm. and a gestational age of less than 38 weeks are used frequently as indications of prematurity.

RESULTS[4]

Association of Presence of Center for Cuboid Bone with Certain Criteria of Infant's Maturity.—Birth Weight: Marked positive associa-

3. Dunham, E. C.; Jenss, R. M., and Christie, A. U.: A Consideration of Race and Sex in Relation to the Growth and Development of Infants, J. Pediat. **14**:156-160 (Feb.) 1939.

4. The data given in this report refer to the center for the right side only. Additional analyses indicate that they also apply to the left side—that there is no asymmetry in the development of the center.

tion was found between the presence of the center for the cuboid bone and the birth weight of the infants in each race—sex group—white boys, white girls, Negro boys and Negro girls; the center was present more frequently in infants of higher birth weight than in those of lower birth weight (table 1). For example, among the white boys the center was present in only 4 per cent of those of the lowest weight group (less than 2,500 Gm.), in 34 per cent of those in the intermediate group (2,500 to 3,499 Gm.) and in 49 per cent of the infants weighing 3,500 Gm. or more.

TABLE 1.—*Percentage of 1,107 Infants* Distributed According to Race, Sex and Maturity in Whom the Center for the Cuboid Bone (Right Side) Was Present*

	White				Negro			
	Boys		Girls		Boys		Girls	
Criterion of Maturity	Total No	Percentage with Center Present	Total No.	Percentage with Center Present	Total No.	Percentage with Center Present	Total No.	Percentage with Center Present
Birth weight, in grams								
Less than 2,500	27	3.7	30	30.0	37	16.2	46	32.6
2,500 to 3,499	147	34.0	161	62.7	173	52.0	204	73.0
3,500 or more	128	48.8	75	72.0	58	75.9	26	80.8
Birth length, in centimeters								
Less than 47	37	5.4	44	36.4	67	22.4	75	46.7
47 to 49.9	110	40.0	132	65.2	129	57.4	163	74.2
50 or more	150	43.3	90	68.9	72	70.8	38	76.3
Gestational age, in weeks †								
Less than 38	58	19.0	45	51.1	91	36.3	77	50.6
38 to 41	200	41.0	178	66.9	144	59.0	168	73.2
42 or more	37	48.6	38	50.0	27	70.4	24	83.3

* These children were born alive to mothers delivered in the ward service of the Johns Hopkins Hospital during parts of 1936, 1937 and 1938 and were examined roentgenographically within seventy-two hours of birth.

† For 2 white boys, 5 white girls, 6 Negro boys and 7 Negro girls among the 1,107 infants studied the gestational age was unknown.

Crown-Heel Length at Birth: A marked positive association was found also between the presence of the center for the cuboid bone and the crown-heel length at birth of the infants in each race-sex group (table 1). For example, among the Negro boys the center was present in only 22 per cent of those with the shortest crown-heel length (less than 47 cm.), in 57 per cent of those in the intermediate group (47 to 49.9 cm.) and in 71 per cent of the infants with a crown-heel length at birth of 50 cm. or more.

Gestational Age: A positive association was found between gestational age and the presence of the center for the cuboid bone except among the white girls with a gestational age of 42 weeks or more (table 1). For example, among the Negro girls the center was present in 51 per cent of those of the least gestational age (less than 38 weeks), in 73 per cent of those in the intermediate group (38 to 41 weeks) and in 83 per cent of those of a gestational age of 42 weeks or more.

Summary: In newborn infants of a given race and sex, a marked positive association was found between their maturity as indicated by each of three criteria—birth weight, crown-heel length at birth and gestational age—and their osseous development at birth as indicated by the presence of the center of ossification for the cuboid bone. The infants of higher birth weight, of greater crown-heel length at birth and of greater gestational age all had the center present more frequently than did those of lower birth weight, of shorter crown-heel length at birth and of lower gestational age.

Association of Presence of Center for Cuboid Bone with Parity and Age of Mother.—The data were also examined to determine whether any association existed between the osseous development of the infant and the parity and age of the mother. In order to measure this association as accurately as possible, the analyses were limited to infants of the same race and sex and of similar maturity according to each of the three criteria previously used in this study, that is, birth weight, crown-heel length at birth and gestational age. The results of these analyses are given in tables 2, 3, 4 and 5.[4a]

Parity of Mother: All mothers. Table 2 shows for each race-sex group of infants, in relation to the parity of the mothers, the percentage of infants of similar maturity according to the three criteria in whom the center for the cuboid bone was present. No consistent association was found between the parity of the mother and the development of the center in the infant. For example, among the Negro boys in the intermediate birth weight group (2,500 to 3,499 Gm.) the center was present in a somewhat greater percentage of the infants born to primiparas (53 per cent) than in those born to multiparas (51 per cent), whereas among the Negro girls in the same weight group the reverse was true; that is, the center was present in a greater percentage of infants born to multiparas (75 per cent) than in those born to primiparas (72 per cent).

Mothers with no complications of pregnancy. It was thought possible that complications of the mother's pregnancy might influence the osseous development of the infant and that if the infants whose mothers had complications were excluded an association between parity and skeletal development might be found. Therefore, an analysis of the figures was made, with the infants of such mothers excluded, as shown in table 3.

It was found that among the infants born to mothers with no complications those born to primiparas had the center for the cuboid bone

4a. In analyzing the figures for each pair of contrasting groups the trend or direction of the difference between the percentages was studied, rather than the magnitude of the difference. Analysis of the magnitude of the difference was not considered justifiable, since some of the percentages were based on a small number of observations.

TABLE 2.—*Percentage of 1,107 Infants * in Whom the Center for the Cuboid Bone (Right Side) Was Present Distributed According to Race, Sex and Maturity and Parity of the Mother*

Criterion of Maturity	White Boys Born to				White Girls Born to				Negro Boys Born to				Negro Girls Born to			
	Primiparas		Multiparas		Primiparas		Multiparas		Primiparas		Multiparas		Primiparas		Multiparas	
	Total No.	Percentage with Center Present	Total No.	Percentage with Center Present	Total No.	Percentage with Center Present	Total No.	Percentage with Center Present	Total No.	Percentage with Center Present	Total No.	Percentage with Center Present	Total No.	Percentage with Center Present	Total No.	Percentage with Center Present
Birth weight, in grams																
Less than 2,500	19	5.3	8	0.0	20	35.0	10	20.0	22	4.5	15	33.3	33	36.4	13	23.1
2,500 to 3,499	90	34.4	57	33.3	93	62.4	68	63.2	102	52.9	71	50.7	133	72.2	71	74.6
3,500 or more	55	50.9	68	47.1	31	64.5	44	77.3	22	68.2	36	80.6	10	80.0	16	81.2
Birth length, in centimeters																
Less than 47	25	8.0	12	0.0	27	40.7	17	29.4	47	25.5	20	15.0	55	49.1	20	40.0
47 to 49.9	70	40.0	40	40.0	72	62.5	60	68.3	59	55.9	70	58.6	101	73.3	62	75.8
50 or more	69	43.5	81	43.2	45	64.4	45	73.3	40	62.5	32	81.2	20	75.0	18	77.8
Gestational age, in weeks †																
Less than 38	37	13.5	21	28.6	26	53.8	19	47.4	51	27.4	40	47.5	53	52.8	24	45.8
38 to 41	112	44.6	88	36.4	93	63.4	85	70.6	75	60.0	69	58.0	107	72.9	61	73.8
42 or more	14	35.7	23	56.5	24	50.0	14	50.0	17	58.8	10	90.0	13	69.2	11	100.0

* These children were born alive to mothers delivered in the ward service of the Johns Hopkins Hospital during parts of 1936, 1937 and 1938 and were studied roentgenographically within seventy-two hours of birth.

† For 2 white boys, 5 white girls, 6 Negro boys and 7 Negro girls among the 1,107 infants studied the gestational age was unknown.

TABLE 3.—*Percentage of 572 Infants* in Whom the Center for the Cuboid Bone (Right Side) Was Present Born of Mothers Who Had No Complication of Pregnancy, Distributed According to Race, Sex and Maturity and Parity of the Mother*

Criterion of Maturity	White Boys Born to				White Girls Born to				Negro Boys Born to				Negro Girls Born to			
	Primiparas		Multiparas		Primiparas		Multiparas		Primiparas		Multiparas		Primiparas		Multiparas	
	Total No.	Percentage with Center Present	Total No.	Percentage with Center Present	Total No.	Percentage with Center Present	Total No.	Percentage with Center Present	Total No.	Percentage with Center Present	Total No.	Percentage with Center Present	Total No.	Percentage with Center Present	Total No.	Percentage with Center Present
Birth weight, in grams																
Less than 2,500	10	0.0	3	0.0	12	50.0	4	0.0	10	0.0	5	20.0	15	33.3	3	33.3
2,500 to 3,499	59	37.3	33	39.4	56	62.5	37	73.0	44	40.9	25	44.0	80	67.5	34	76.5
3,500 or more	29	55.2	33	57.6	21	61.9	26	76.9	8	75.0	17	94.1	6	83.3	2	100.0
Birth length, in centimeters																
Less than 47	14	7.1	5	0.0	16	56.2	6	16.7	20	10.0	6	16.7	30	43.3	4	50.0
47 to 49.9	39	41.0	25	40.0	43	62.8	36	77.8	27	55.6	26	53.8	57	70.2	30	76.7
50 or more	45	46.7	39	56.4	30	60.0	25	72.0	15	46.7	15	86.7	14	78.6	5	80.0
Gestational age, in weeks †																
Less than 38	21	19.0	9	33.3	16	75.0	7	57.1	23	17.4	16	56.2	34	47.1	8	62.5
38 to 41	69	44.9	49	44.9	54	63.0	51	72.5	30	50.0	28	60.7	57	73.7	26	73.1
42 or more	7	42.9	10	70.0	18	44.4	7	57.1	8	62.5	3	66.7	7	71.4	4	100.0

* These children were born alive to mothers delivered in the ward service of the Johns Hopkins Hospital during parts of 1936, 1937 and 1938 and were studied roentgenographically within seventy-two hours of birth.

† Among the 572 infants studied, there were 2 white boys, 3 white girls, 1 Negro boy and 4 Negro girls for whom the gestational age was unknown.

TABLE 4.—*Percentage of 1,107 Infants* in Whom the Center for the Cuboid Bone (Right Side) Was Present and Distributed According to Race, Sex and Maturity and Age of the Mother*

Criterion of Maturity	White Boys Born to Mothers of				White Girls Born to Mothers of				Negro Boys Born to Mothers of				Negro Girls Born to Mothers of			
	Less Than 20 Years		20 Years or More		Less Than 20 Years		20 Years or More		Less Than 20 Years		20 Years or More		Less Than 20 Years		20 Years or More	
	Total No.	Percentage with Center Present	Total No.	Percentage with Center Present	Total No.	Percentage with Center Present	Total No.	Percentage with Center Present	Total No.	Percentage with Center Present	Total No.	Percentage with Center Present	Total No.	Percentage with Center Present	Total No.	Percentage with Center Present
Birth weight, in grams																
Less than 2,500	7	0.0	20	5.0	9	22.2	21	33.3	21	4.8	16	31.2	25	36.0	21	28.6
2,500 to 3,499	68	26.5	79	40.5	42	59.5	119	63.9	76	52.6	97	51.5	102	69.6	102	70.5
3,500 or more	28	53.6	95	47.4	15	60.0	60	75.0	18	61.1	40	82.5	9	88.9	17	76.5
Birth length, in centimeters																
Less than 47	13	0.0	24	8.3	13	30.8	31	38.7	43	23.3	24	20.8	45	48.9	30	43.3
47 to 49.9	46	34.8	64	43.8	37	62.2	95	66.3	46	54.3	83	59.0	77	70.1	86	77.9
50 or more	44	38.6	106	45.3	16	56.2	74	71.6	26	65.4	46	73.9	14	85.7	24	70.8
Gestational age, in weeks †																
Less than 38	25	24.0	33	15.2	12	58.3	33	48.5	43	20.9	48	50.0	44	54.5	33	45.5
38 to 41	66	36.4	134	43.3	41	61.0	137	68.6	58	62.1	86	57.0	80	71.2	88	75.0
42 or more	11	27.3	26	57.7	11	27.3	27	59.3	11	54.5	16	81.2	9	66.7	15	93.3

* These children were born alive to mothers delivered in the ward service of the Johns Hopkins Hospital during parts of 1936, 1937 and 1938 and were studied roentgenographically within seventy-two hours of birth.

† Of the 1,107 infants studied, the gestational age was unknown for 2 white boys, 5 white girls, 6 Negro boys and 7 Negro girls.

TABLE 5.—*Percentage of 572 Infants* in Whom the Center for the Cuboid Bone (Right Side) Was Present Born of Mothers Who Had No Complication of Pregnancy, Distributed According to Race and Sex and Maturity and Age of the Mother*

Criterion of Maturity	White Boys Born to Mothers of				White Girls Born to Mothers of				Negro Boys Born to Mothers of				Negro Girls Born to Mothers of			
	Less Than 20 Years		20 Years or More		Less Than 20 Years		20 Years or More		Less Than 20 Years		20 Years or More		Less Than 20 Years		20 Years or More	
	Total No.	Percentage with Center Present	Total No.	Percentage with Center Present	Total No.	Percentage with Center Present	Total No.	Percentage with Center Present	Total No.	Percentage with Center Present	Total No.	Percentage with Center Present	Total No.	Percentage with Center Present	Total No.	Percentage with Center Present
Birth weight, in grams																
Less than 2,500	5	0.0	8	0.0	6	33.3	10	40.0	11	0.0	4	25.0	13	38.5	5	20.0
2,500 to 3,499	45	26.7	47	48.9	25	56.0	68	70.6	34	35.3	35	48.6	58	67.2	56	73.2
3,500 or more	15	60.0	47	55.3	10	50.0	37	75.7	5	80.0	20	90.0	6	83.3	2	100.0
Birth length, in centimeters																
Less than 47	9	0.0	10	10.0	8	37.5	14	50.0	21	9.5	5	20.0	26	46.2	8	37.5
47 to 49.9	26	38.5	38	42.1	23	56.5	56	75.0	20	45.0	33	60.6	39	69.2	48	75.0
50 or more	30	36.7	54	59.3	10	50.0	45	68.9	9	55.6	21	71.4	12	83.3	7	71.4
Gestational age, in weeks †																
Less than 38	14	28.6	16	18.8	8	62.5	15	73.3	25	20.0	14	57.1	31	51.6	11	45.5
38 to 41	43	37.2	75	49.3	24	58.3	81	70.4	18	38.9	40	62.5	39	74.4	44	72.7
42 or more	7	14.3	10	90.0	8	25.0	17	58.8	6	66.7	5	60.0	4	75.0	7	85.7

* These children were born alive to mothers delivered in the ward service of the Johns Hopkins Hospital during parts of 1936, 1937 and 1938 and were studied roentgenographically within seventy-two hours of birth.

† Of the 572 infants studied, the gestational age was unknown for 2 white boys, 3 white girls, 1 Negro boy and 4 Negro girls.

present less frequently than did those born to multiparas.[5] For example, among such infants with a crown-heel length at birth of 50 cm. or more, the center was present in 56 per cent of the white boys born to multiparas as compared with 47 per cent born to primiparas and in 72 per cent of the white girls born to multiparas as compared with 60 per cent born to primiparas. Corresponding figures for Negro infants are: 87 and 47 per cent for boys and 80 and 79 per cent for girls.

No similar analysis was made for infants whose mothers had had complications of pregnancy, because the number of such women was too small to permit study of the different types of complication separately and because neither the time of onset nor the severity of all the complications was known.

Age of Mother: All mothers. Table 4 shows for each race-sex group the age of the mothers and the maturity of the infants in relation to the presence of the center for the cuboid bone. In general, a positive association was found to exist between the development of the cuboid bone in the infant and the age of the mother.[6] For example, among Negro boys of the least gestational age (less than 38 weeks) the center for the cuboid bone was present in 50 per cent of the infants born to the older women (20 years of age or more) as compared with 21 per cent of those born to the younger women (less than 20 years).

Mothers with no complications of pregnancy. In order to allow for the possible influence of complications of pregnancy among women in the two age groups, the data for infants born to women who had had no complications of pregnancy were analyzed separately, as is shown in table 5. When only the infants born to women without complications of pregnancy were studied,[7] an even closer association was found between the osseous development of the infant and the age of the mother.

No similar analysis was made for infants whose mothers had had complications of pregnancy, for the reasons given in the discussion on parity.

The apparently closer association of the presence of the center for the cuboid bone with the age of the mother than with her parity may be due in part to the fact that the classification of mothers by age was done on a more exact basis than the classification by parity, for each mother's age

5. This statement holds for twenty-six of thirty-six comparisons (72.2 per cent). For three comparisons the difference was zero.

6. This statement holds for twenty-five of thirty-six comparisons (69.4 per cent).

7. This statement holds for twenty-seven of thirty-six comparisons (75 per cent). For one comparison the difference was zero. The average difference for all infants was 7.1 per cent, and for infants whose mothers had had no complications, 11.7 per cent.

was recorded in completed years, whereas her parity was recorded merely by describing her as a "primipara" or a "multipara," without differentiating secundiparas, triparas, and so forth.[8]

REVIEW OF LITERATURE

The literature contains reports of a number of studies of the osseous development of newborn infants, but most of these investigations are not comparable with the present one. For example, Adair and Scammon [9] did not take the infant's birth weight into account, and besides, they combined their data with observations collected by workers reporting from other countries over a number of years. Menees and Holly [10] made their observations on a group of infants selected in such a way that certain prematurely born infants were excluded from the group, if prematurity is judged in terms of the infant's birth weight, crown-heel length at birth or gestational age. Stuart [11] included only infants weighing more than 5 pounds (2,267 Gm.) at birth. Vogt and Vickers [12] presented graphic data, based on Stuart's material, for infants of slow, average or advanced development only. Stampfel and Tscherne [13] reported observations on a relatively small number of infants in another country, not all of whom were selected by the same criterion of maturity. According to these authors, the size of a center is probably a better criterion of maturity than the presence of the center, and the best centers for use in judging the maturity of an infant, even in utero, are the proximal epiphysis of the tibia and the "medial humerus."

SUMMARY

In a study of the osseous development of 1,107 newborn infants—297 white boys, 266 white girls, 268 Negro boys and 276 Negro girls—born alive between May 1936 and December 1938 to women who were patients in the obstetric wards of the Johns Hopkins Hospital, roent-

8. This is shown also when the size as well as the direction of the differences is taken into account. The resulting average differences for mothers with no complications are: by parity, 6.6 per cent; by age of mother, 11.7 per cent.

9. Adair, F. L., and Scammon, R. E.: Ossification Centers of Wrist, Knee and Ankle at Birth, with Particular Reference to Physical Development and Maturity of Newborn, Am. J. Obst. & Gynec. **2**:35-60 (July) 1921.

10. Menees, T. O., and Holly, L. E.: Ossification in Extremities of Newborn, Am. J. Roentgenol. **28**:389-390 (Sept.) 1932.

11. Stuart, H. C.: Standards of Physical Development for Reference in Clinical Appraisement: Suggestions for Their Presentation and Use, J. Pediat. **5**:194-209 (Aug.) 1934.

12. Vogt, E. C., and Vickers, V. S.: Osseous Growth and Development, Radiology **31**:441-444 (Oct.) 1938.

13. Stampfel, K., and Tscherne, E.: Die Röntgendiagnose der übertragenen Frucht, Ztschr. f. Geburtsh. u. Gynäk. **119**:31-44, 1939.

genograms of the infants made within seventy-two hours of birth showed association of the presence of the center of ossification for the cuboid bone (right side) with race and sex, with certain often used criteria of the maturity of the infant and with the parity and age of the mother, as follows:

1. The development of the center of ossification for the cuboid bone was found to vary with race and sex. The center was found to be present more frequently in Negro than in white infants of the same sex. In both Negro and white children it was found to be present more frequently in girls than in boys.

2. For infants of a given race and sex the center was found to be present more frequently in the infants who were judged more mature than in those who were judged less mature, according to each of three criteria, namely, birth weight, crown-heel length at birth and gestational age.

3. Among infants born to women with no complications of pregnancy the development of the center was found to be more advanced in those born to multiparas than in those born to primiparas.

4. The development of the center was more advanced among infants born to the older women (20 years of age or more). This association with the age of the mother was more marked when only infants born to mothers with no complications of pregnancy were studied.

Dr. Edwards A. Park, professor of pediatrics, Dr. Nicholson J. Eastman, professor of obstetrics, and Dr. J. William Pierson, associate professor of roentgenology, of the Johns Hopkins University School of Medicine, made this study possible.

ENCEPHALITIS COMPLICATING MEASLES

A REPORT ON TWO HUNDRED AND FORTY-ONE CASES COLLECTED FROM THE LITERATURE AND ON FORTY-FOUR ADDITIONAL CASES

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When the virus of measles attacks the central nervous system the resulting clinical picture has one outstanding characteristic, namely, variability. Results of physical examinations and laboratory tests are so bizarre and inconstant that in respect to them one case has little in common with another, save that all results indicate involvement of the central nervous system. No more specific common denominator is available.

Encephalitis complicating measles has long been known and reported, but in no instance has any considerable series of cases been analyzed by a single observer; consequently, the clinical data have been limited to the observations in small groups of cases. Even terminology has been confused, because the widely varying clinical picture tends to encourage nomenclature descriptive of individual observations. Thus one finds "encephalitis," "encephalomeningitis," "serous meningitis," "paraplegia," "meningoencephalitis" and other terms used in case reports. Because the term encephalitis seems best fitted to the condition in the large majority of cases and to avoid confusion, we shall use it, even though in an occasional case it is not the best descriptive name.

REPORT OF STUDY

This report is an attempt to correlate the findings in 241 cases reported by 110 authors during the past decade, together with data from 44 other cases observed by us. Naturally, such a study cannot be statistically accurate, both because the number of cases is too small for statistical significance and because many items were not mentioned in all the cases recorded, but it may shed some light on a confused subject which seems to be assuming increasing importance.

From the University of Southern California School of Medicine and the Communicable Disease Unit, Los Angeles County Hospital.

Incidence.—The incidence of encephalitis complicating measles is not known and may never be known exactly, since the reporting of cases of measles is notoriously inaccurate and the cases of mild encephalitis may well be missed or not reported. At least a few cases should be expected in epidemics of measles in any city of considerable size, for according to Hoyne the older estimate of 1 case of encephalitis per thousand cases of measles was borne out by the incidence of encephalitis in the epidemic of measles in Chicago in 1938. In our own experience this figure should be somewhat higher.

Pathogenesis.—The pathogenesis is not known, and since in this paper we are dealing only with the clinical aspects of the condition, the various theories of causation, such as hypersensitivity, allergic reaction to the virus or its products or infection with neurotropic strains of the virus, will not be discussed. Suffice it to say that we have found no evidence of predisposition connected with the severity of the infection,

TABLE 1.—*Age Incidence of Encephalitis Complicating Measles*

	Age, Years									
	Under 1	1-2	2-4	5-7	8-10	11-13	14-16	17-20	21-25	Over 25
Our cases.....	0	1	6	18	8	7	1	0	1	2
Reported cases *.....	5	14	66	77	35	12	10	6	6	7
Total.....	5	15	72	95	43	19	11	6	7	9

* In 3 cases the age was not stated.

the age, the sex, the race or body type of the patient, the season or other factors, either in our own cases or in those reviewed.

Pathologic Changes.—They are for the most part of vascular origin, either directly or indirectly. Hyperemia, engorgement and hemorrhage are seen in the meninges, the spinal cord or the brain, the hemorrhages usually, but not always, being petechial; the blood vessels have thickened walls, and the perivascular regions show an infiltration or proliferation of cells which forms a cuff. By special staining technics these proliferated cells may be shown to be largely microglial cells rather than the expected lymphocytes, monocytes and granulocytes. Complete pathologic studies have been made by Finley, Moore and McCordock, Ferraro and Scheffer and others.

Age Incidence.—The age incidence closely parallels that of measles, as would be expected (table 1). Thus, over one half of the cases occur between 2 and 8 years and about one-third between 5 and 7 years of age. In our own cases the average age was slightly above that in the cases collected from the literature, being 8.9 years as compared with 7.3 years. No age at which measles occurs is spared.

Onset.—The encephalitis may precede the measles rash or even precede the first symptoms of invasion; it may occur with the rash or appear at varying periods after it. In our own cases encephalitis always appeared after the rash save in 1 instance, in which symptoms began five days before the rash. The average time elapsed after appearance of the rash before the onset of encephalitic symptoms in our cases was two and seven-tenths days, as compared with five and two-tenths days in the cases reviewed. The longest time in our cases was eleven days, though cases have been reported in which symptoms of encephalitis appeared as long as a month or six weeks after the rash; these possibly should be accepted as instances of encephalitis complicating measles with some reservation. Onset prior to the appearance of rash is rare, but it occurred in 16 of the series of cases collected from the literature; in all but 1 case (in which there was a lapse of nine days) the rash appeared within six days. An additional case has been excluded, as the encephalitis was reported to have begun eighteen days before the rash; in this case, it seems that encephalitis must have begun even before the patient was exposed to measles and therefore must have had some causation other than measles. The other extreme in time of onset, six weeks after the rash, may also be questioned.

Symptoms.—Symptoms vary tremendously, according to the severity of the involvement and the portion of the nervous system most severely attacked. Fever is usual though not invariable; sometimes the temperature is very high, and fever may appear in a patient previously afebrile for several days. Duration of the fever is not consistently related to other factors. Changes in the sensorium almost always occur, usually indicated by torpor and lethargy, which often deepen into coma, but occasionally by restlessness, excitement and disorientation (table 2).

Results of the various neurologic examinations are varied and bizarre, often without seeming relation to one another and sometimes varying widely from day to day. The reflexes and meningeal signs noted are shown in table 3.

Onset may be gradual, with lethargy deepening into coma, or it may be abrupt; changes in the sensorium may either precede or follow the convulsive state and may last from a short period to as long as two months.

Convulsive seizures may be clonic or tonic, generalized or jacksonian, and may begin in any part of the body. They occur most frequently at the onset, next oftenest as a terminal event and are rarely continuous save in the cases of rapidly fatal termination.

Irritability, irrationality, delirium, listlessness, psychosis, mania, negativism, catatonia, changes in the sleep mechanism and memory

defects in varying intensity occur singly or in combination in most cases. These symptoms may regress, recur, remain or entirely disappear.

The cranial nerves are more commonly affected than the peripheral nerves, though involvement of the latter may occur. Effects of involve-

TABLE 2.—*Symptoms Occurring in Two Hundred and Eighty-Five Cases of Encephalitis Complicating Measles*

Symptom	Cases Collected from Literature (241)	Our Cases (44)	Total (285)
Sensorium:			
Coma	68	22	90
Stupor	46	8	54
Lethargy	59	30	89
Delirium	18	5	23
Irrationality and confusion	8	6	14
Irritability	29	7	36
Memory defect	12	0	12
Psychosis	6	3	9
Headache	24	3	27
Convulsions	91	24	115
Cranial nerves:			
Squint and strabismus	16	1	17
Aphonia and aphasia	33	0	33
Speech defect	8	2	10
Trismus	11	0	11
Diplopia and conjugate deviation	7	0	7
Nuclear paralysis, third nerve	1	0	1
Nuclear paralysis, fifth nerve	1	0	1
Nuclear paralysis, sixth nerve	1	0	1
Deafness	1	0	1
Visual loss and defect	3	0	3
Nystagmus	22	4	26
Optic neuritis	3	0	3
Ptosis	13	0	13
Hippus	12	0	12
Papilledema	3	0	3
Inequality of pupils	9	3	12
Dilatation of pupils	21	0	21
Fixation of pupils	18	4	22
Contraction of pupils	4	0	4
Sluggish response of pupils	14	4	18
Lagophthalmos	1	0	1
Pain in eyes	1	0	1
Facial twitching	4	10	14
Facial paralysis	12	3	15
Facial hyperesthesia	1	0	1
Bulbar paralysis	18	5	23
Diaphragmatic paralysis	8	0	8
Peripheral nerves:			
Tremor	23	1	24
Ataxia	21	0	21
Paralysis	121	5	126
Paresis	23	8	31
Visceral nerves:			
Incontinence	25	11	36
Involuntary urination	12	3	15
Retention	21	10	31
Sensory nerves:			
Pain	10	2	12
Hyperesthesia	5	10	15
Hypesthesia	5	2	7
Anesthesia	11	4	15
Paresthesia	8	0	8

ment of the cranial nerves include aphonia and speech defects, ocular disturbances of all sorts, deafness, blindness and facial or bulbar paralysis. One or more of these changes is likely to be found in each case. Results of changes in the peripheral nerves vary from the minor involve-

ment of a single muscle to complete paraplegia. Involvement of the visceral nerves is usually reflected in such signs of malfunction of the bladder as incontinence, dribbling or retention of urine or involuntary urination.

Other physical abnormalities consist largely of changes in the reflexes. In many of the cases reviewed the status of the reflexes was not noted; so the number of changes probably was greater than table 3 indicates. The deep, or tendon, reflexes are usually changed in cases in which there is involvement of the spinal cord; they may be normal, hypoactive, hyperactive, absent or show clonus, and the picture may vary from day to day. Superficial, or cutaneous reflexes are usually

TABLE 3.—*Changes in Reflexes and Meningeal Signs Occurring in Two Hundred and Eighty-Five Cases of Encephalitis Complicating Measles*

	Cases Collected from Literature (241)	Our Cases (44)	Total (285)
Deep reflexes:			
Hyperactive	41	10	51
Normal	1	12	13
Hypoactive	48	24	72
Unequal	5	0	5
Superficial reflexes:			
Hyperactive	23	0	23
Normal	1	0	1
Hypoactive	24	31	55
Unequal	4	6	10
Clonus	10	1	11
Babinski	43	17	60
Meningeal signs:			
Kernig	47	20	67
Brudzinski	17	17	34
Stiff neck	59	28	87
Stiff spine	3	15	18

hypoactive or absent and are often unequal on the two sides. The Babinski sign may or may not be elicited. Signs of meningeal irritation are commonly present; often in the reports of cases the term opisthotonos appears, with no mention of the individual signs of meningeal irritation, which may explain the relatively higher incidence of these signs in our series of cases. The most common single sign is stiffness of the neck and the one next most frequent is the Kernig sign.

Laboratory Data.—Results of laboratory procedures share the variability and inconsistency of the other factors already mentioned. Naturally, interest centers in the results of examinations of the spinal fluid, in which some deviation from normal is expected, though there is no constant or pathognomonic change (table 4). The spinal fluid may be entirely normal and under normal pressure at some stage of the disease, but repeated examination usually shows some definite change or changes.

Data on the cases collected from the literature do not differ enough from those given in table 4 to warrant separate tabulation. In over half the cases there were 300 cells or less per cubic millimeter; in 1 instance, as well as in 1 case of our own, the cells were all polymorphonuclears. Almost all investigators reported an increase in pressure, though in many instances the pressure was not stated. Nontraumatic hemorrhage into the spinal canal may occasionally occur from rupture of small engorged vessels, as was shown by postmortem examination in 1 of our cases. Chemical changes are usually absent or are limited to an increase in globulin. Results of quantitative determinations of globulin in 21 cases averaged 86 mg. per hundred cubic centimeters; the lowest value was 20 mg. and the highest 320 mg., with the value in 5 others between 100 and 200 mg. The average sugar content reported was 79 mg. per hundred cubic centimeters of spinal fluid.

TABLE 4.—*Results of Examination of the Spinal Fluid on Admission in Forty-Four Cases of Encephalitis Complicating Measles*

	High	Low	Average
Pressure, mm.	400	100	225
Cell count, per cu. mm.	700	0	131
Percentage of lymphocytes	100	0	81
Chlorides, mg. per 100 cc.	730	510	645
Reaction to test for globulin (Pandy)	17 positive	25 negative	
Sugar content	20 increased	4 decreased	9 normal

White Cell Count.—The leukocyte count would be expected to be low, since measles itself and other forms of encephalitis tend to produce slight leukocytosis or actual leukopenia. This, however, is usually not the case, although Peterman and Fox reported leukopenia (2,800 leukocytes per cubic millimeter) in 1 case. The lowest white cell count in our cases was 7,000, and the average for the 43 counts reported plus those for our own cases was 16,130, with 80 per cent polymorphonuclears. The highest counts reported were 40,900, by Peterman and Fox, and 45,000 by Ferraro and Scheffer; our two highest counts were 30,000 and 33,400.

Prognosis.—The prognosis for life in any individual case is uncertain, as the disease may progress, regress or remain stationary. The blood count seems to have little or no significance; both the patients with leukopenia previously mentioned recovered, and 2 of the 4 patients with extreme leukocytosis died. Hyperpyrexia of rapid onset, with constant increase, was present in about half of the fatal cases; progressive bulbar paralysis is also a serious symptom. Very young patients seem to have the poorer prognosis; otherwise, the age incidence of mortality closely parallels that of the disease.

The prognosis for sequelae is also uncertain and is finally determined entirely by observation of the individual patient. Any of the neurologic symptoms listed in table 2 may become permanent or may persist for a long time before recovery ensues. The figures for the incidence of sequelae are inadequate, both in our own cases and in those collected from the literature, because of insufficient follow-up of patients after discharge from the hospital. The data we have are given in table 5.

TABLE 5.—*Mortality and Residual Symptoms in Two Hundred and Eighty-Five Cases of Encephalitis Complicating Measles*

	Cases Collected from Literature (241)	Our Cases (44)	Total (285)
Residual symptoms of more than ten weeks' duration	100	15	115
Complete recovery	94	18	112
Death	47	11	58
Mental defect	22	7	29
Ataxia	22	0	22
Spasticity	20	0	20
Fixation of pupils	20	0	20
Pareses	15	1	16
Paralyses	9	5	14
Aphasia	8	0	8
Speech defect	7	0	7
Idiocy	6	0	6
Convulsive state	6	0	6
No statement	6	0	6
Atrophy	4	0	4
Personality changes	3	0	3
Chorea	3	0	3
Sexual precocity	3	0	3
Irritability	2	0	2
Scanning speech	2	0	2
Narcolepsy	2	0	2
Ophthalmoplegia	2	0	2
Athetosis	2	0	2
Recurrence after recovery	2	0	2
Excitability	1	0	1
Confusion	1	0	1
Nystagmus	1	0	1
Blindness	1	0	1
Pain	1	0	1
Hyperesthesia	1	0	1
Cord bladder	1	0	1
Urinary retention	1	0	1
Diabetes insipidus	1	0	1
Anesthesia	0	1	1

Residual symptoms do not seem especially likely to occur in patients with a severe acute phase of the illness. In our own cases severe mental damage was more common than it was in the cases collected from the literature, and minor mental derangement was less frequent. Severe paralysis or paresis tends to remain in about 10 per cent of the cases, and convulsive states and choreiform or athetoid movements, in about 5 per cent. The minor defects which remain are usually pupillary changes, aphasia and speech defects; less frequent are sensory changes and such evidences of involvement of the autonomic and endocrine systems as sexual precocity, obesity or diabetes insipidus.

In general then, the prognosis may be roughly estimated as follows: of 10 patients, 4 will recover completely, 2 will die and 4 will have one or more major or minor debilitating residual symptoms.

Diagnosis.—Making the diagnosis is relatively easy in the presence of a measles epidemic or after a known attack of measles. In other circumstances it may be difficult or even impossible, and in the case of encephalitis appearing prior to recognizable symptoms of measles it must wait until such symptoms appear.

Therapy.—Therapy other than that which is symptomatic is scarcely mentioned in the literature. A few European authors have mentioned such procedures as fixation abscess therapy, transfusions and immunotransfusions but with no comment as to their effectiveness. Benzedrine sulfate was employed by Revel in a case of long-continued coma, and Storts used repeated intrathecal injections of convalescent serum. A number of other drugs have been used, including strychnine, sodium salicylate and methenamine, none of which yielded definite results. Our own attempts at therapy fall roughly into three groups:

Group I. Eighteen patients received symptomatic treatment, with the following results:

Three patients made rapid, uneventful recoveries within seventy-two hours, with no residual symptoms. Four patients attained complete recovery in one week, 1 in two weeks and 2 in more than two weeks. One patient left the hospital against advice, with no improvement at the end of a week. Two left the hospital with paresis of the extremities. Five died.

Group II. Ten patients received one or more of the following: convalescent measles serum, human convalescent poliomyelitis serum and immunotransfusion with these results:

Four recovered without residual symptoms by the end of the first week. One recovered completely but not until the end of the sixth week. Five died.

Group III. Sixteen patients were given shock therapy by intravenous injection of commercial mixed typhoid vaccine. The first patients were given a dose of 10,000,000 bacteria, which produced a rapid but slight rise in temperature; the dose was then increased to 50,000,000 and in some cases, particularly when we were attempting a second treatment (which was never completely successful), to as much as 200,000,000 bacteria. The febrile response was variable, the rise in temperature being 7 degrees F. in 1 case, 6 degrees in 1, 5 degrees in 2, 4 degrees in 2, 3 degrees in 8, 2 degrees in 5, and less than 2 degrees in 1, including those cases in which treatment was given more than once. The peak temperature was of short duration, the length of time varying from fifteen to forty-five minutes, but the temperature did not return

permanently to the previous level for about twelve hours. The height of the fever did not seem directly correlated with the results, except that elevations of temperature of less than 3 degrees F. never produced any noticeable results. More prolonged fever might logically be expected to yield better results, but we have had no facilities with which to test its effect. Treatment of these 16 patients gave these results: Three recovered completely within seventy-two hours. Two recovered within one week, 1 in two weeks, 1 in three weeks and 2 in four to six weeks. Four could not be followed satisfactorily to determine results: 1 was transferred to another hospital on the fifth day, 1 was taken home against advice in thirty-six hours and 2 others were similarly taken home on the eleventh and the fifteenth day, still showing evidence of the disease. Two recovered, with residual symptoms: 1 had mental impairment and paralysis, and the other was an imbecile. One died.

In this group 8 patients also received therapy of the type given the patients in group II. In each instance the shock treatment was used after the previous treatment had seemed to fail, and it was followed by good recovery in 3 instances, some improvement in 3 and no results in 2.

These figures do not support any definite claims for the value of these methods of treatment, either for the preservation of life or for the prevention of sequelae. Bedside observations of the effects of treatment on the patients in group III have made us cling to shock therapy as a possibly effective treatment, since most of the patients who improved at all did so in such abrupt and dramatic fashion that some sort of causal relation between therapy and clinical results is strongly suggested. Experience in treating patients with encephalitis following other infections and 3 patients with transverse myelitis by means of shock therapy has been similar and lends support to the belief that the improvement seen may not have been coincidence. If shock therapy really does have merit, there remains the question of why it is inconsistent in action. It is not known whether this inconsistency is due to variables in the extent of the shock reaction, to the time in the course of the disease when it is used or to numerous other factors. At present we can offer no answer, but on the basis of our experience we believe shock therapy offers more hope than any other treatment we know of, even administration of convalescent serum, which seems, theoretically at least, to have a more logical basis.

SUMMARY

Data in 241 cases of encephalitis complicating measles collected from the literature and in 44 additional cases of our own are reported.

Either the disease is becoming more common, or it is more generally recognized.

The age incidence and the mortality incidence parallel those of measles.

Symptoms, results of physical examinations and laboratory data vary widely, but they are outlined as far as possible for the 285 cases.

Prognosis can be stated approximately as follows: complete recovery in 40 per cent of cases, recovery with residual symptoms of greater or lesser severity in 40 per cent and death in 20 per cent.

Therapy is unsatisfactory. We have had some encouraging results with shock treatment.

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RELATION OF DENTAL CARIES IN CITY CHILDREN TO SEX, AGE AND ENVIRONMENT

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The amount of solar ultraviolet radiation at a given point on the earth's surface is dependent on its geographic location and on certain climatic and physical variables. It has been demonstrated that vitamin D is created in the human or the animal body when the skin is exposed to ultraviolet radiation, either solar or artificial.[1] Several investigators have reported that children's resistance to dental caries is increased when they are fed vitamin D.[2] McBeath and Zucker [2e] and Erpf [3] have reported that there is a seasonable rhythm in the incidence of caries. They found that the greatest freedom from new caries was in summer, when the most solar ultraviolet energy was available. Summer is also the season when the temperature permits the greatest exposure of the skin to sunshine.

In the study by McBeath and Zucker [2e] the experimental group of children were exposed to artificial ultraviolet radiation during the period

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of greatest susceptibility to caries, winter. This group had significantly less new caries than did the control group, which was not so treated. The children in the control and the experimental group were housed in the same building and were fed the same food. As far as is known, the only difference in the conditions of the two groups used in the experiment was the exposure of the bodies of the children in the experimental group to ultraviolet light, with the consequent production of vitamin D.[4]

In view of the preceding facts and my own experience in dental practice, it occurred to me that the validity of the conclusion—that the ingestion of vitamin D by children had a definitely inhibiting effect on caries formation—could be tested by determining the relation of the incidence of caries in large groups of children to the climatic and the other factors which influence the total amount of solar ultraviolet energy available at the place of residence.

The ultimate total amount of solar ultraviolet energy at a given location on the earth's surface is the product of the intensity of the sun's rays and the duration of the exposure. I have included three environmental factors in this problem which seemed to me to offer the greatest opportunity for the introduction of variables in the amounts of radiant energy available at various localities. Differences in the mean number of hours of sunshine per year introduce the principal variables in duration of exposure, while differences in latitude produce variables in the intensity of the sun's rays, through the effects of air mass. Winter temperature was selected because it was thought to introduce additional factors in the duration of exposure as well as in the intensity of radiation. Low temperatures require the wearing of more clothing. The exposed area of skin is likely to be less in cold than in mild climates.

The first study, in association with Kaiser, was made on rural children.[5] We found that the greater the amount of sunshine and the milder the winter temperature, the lower were the caries rates in the groups of children. On the other hand, the farther north the children resided, the higher were the caries rates.

It seems reasonable that the results obtained in the studies on feeding vitamin D, the observations on the influence of the season on incidence of caries, the effects on caries incidence of the exposure of the skin to ultraviolet light and our results are related.

In the feeding experiments the ingested vitamin D was absorbed from the intestinal tract, and resistance to caries was achieved in that

4. It was assumed that any other action of the ultraviolet energy would have no effect on the incidence of caries.

5. East, B. R., and Kaiser, H.: Relation of Dental Caries in Rural Children to Sex, Age and Environment, Am. J. Dis. Child. **60**:1289 (Dec.) 1940.

manner. The resistance to caries of the children we studied and of those in the experiments with artificial ultraviolet irradiation was the result of the creation of vitamin D in the skin.

Just how this resistance is brought about is not clear. Whether the growth of aciduric bacteria in the mouth is inhibited or whether resistance within the tooth results is not of primary importance from a public health standpoint. The significant point to determine is whether the consumption of vitamin D or the exposure of the skin to the vitamin D–creating rays of the sun does or does not materially reduce the incidence of dental caries.

While our study on rural children established that a relation exists between the incidence of caries and the factors which affect the amount

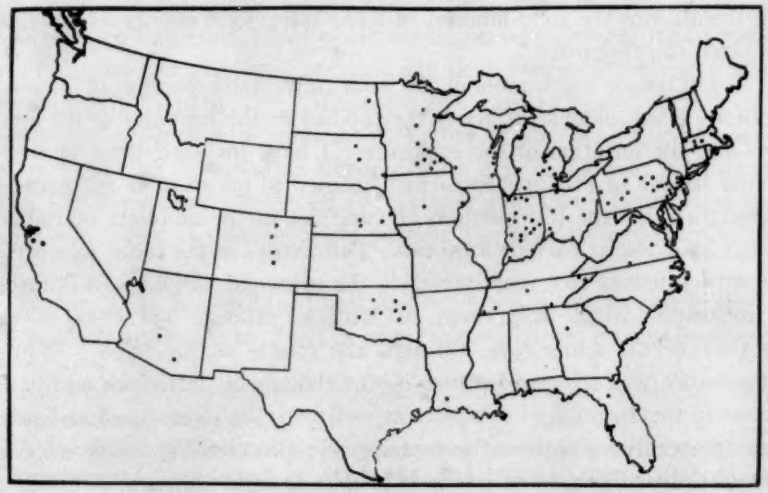

Chart 1.—Geographic distribution of the 130 counties in which are located the 156 cities where the 528,842 children of this study, aged 6 to 14 years, lived.

of solar ultraviolet energy at the place of residence, yet I thought that it might not be possible to demonstrate the same relation for children in larger centers of population. In cities, both private and public prenatal and postnatal medical, dental, nursing and other care is probably, on the whole, better and more generally available than in rural areas. Children in cities are probably exposed to better and more persistent health education than those in the country. It is probably true that, per capita, there are more dentists available, in cities to provide "preventive dentistry" than in the country. The services of free dental clinics are also available to a greater degree in cities than in rural areas. All of these practices and services are intended to and supposedly do

lessen the incidence of caries. On the other hand, housing may be less uniform in cities than in the country, and city housing may be such as to induce more caries. City children are probably less homogeneous, ethnologically, than rural children, and the foods eaten in the city are probably more varied than those consumed in the country. These con-

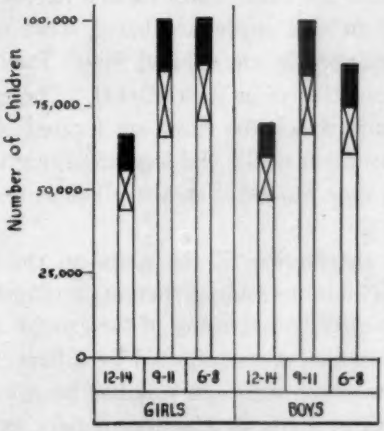

Chart 2.—Distribution of 528,842 children according to age (in years), sex and size of city of residence. Size of city is indicated as a hollow square for those of more than 100,000 population (55 cities); as a crossed square for those between 25,000 and 999,999 population (55 cities) and as a solid square for those between 10,000 and 24,999 population (46 cities).

TABLE 1.—*Distribution by Age and Sex of 528,842 Children in 156 Cities of the United States*

	Boys			Girls			
Age, years	6-8	9-11	12-14	6-8	9-11	12-14	Total
Number of children in 46 cities of 10,000 to 24,999 population	11,781	14,219	10,343	11,766	14,296	9,568	71,973
Number of children in 55 cities of 25,000 to 99,999 population	15,459	18,811	13,764	15,876	18,940	12,394	95,244
Number of children in 55 cities of more than 100,000 population	61,654	67,697	47,809	72,782	66,831	44,852	361,625
Total	88,894	100,727 261,537	71,916	100,424	100,067 267,305	66,814	528,842

ditions might make it impossible to determine the relation of the climatic factors and the incidence of caries in city children in as clearcut a manner as was done in the study on rural children.

The present report deals with dental caries in city children in relation to three environmental factors, the mean number hours of sunshine per year, the mean winter temperature and the latitude. These are the same climatic factors which were considered in the study on rural children. The basic dental data from which I have determined the caries

rates of the city children used in this investigation were collected in the same survey which produced the data for rural children.[5] The method of computing the caries rates has been described elsewhere.[6] The data concerning the climatic variables were collected and published by the United States Weather Bureau.

The data on which the caries rates for the 528,842 white children of 156 cities included in this study are based were collected under the direction of and published by the United States Public Health Service.[7] Each city has a population of at least 10,000. The geographic distribution of the counties in which the cities are located is shown in chart 1. In table 1, the distribution of the children according to sex, age and size of the city in which they resided is shown. The same data are expressed graphically in chart 2.

The frequency distribution of the cities on the basis of the mean caries rates of the children residing therein, arranged according to age and sex to secure greater homogeneity of the groups, is shown in table 2.

When dental data have been collected by different examiners, it is a matter of concern whether sufficient bias has been introduced to invalidate them. One may properly inquire whether the examiners of one city were more skilful or meticulous in locating and recording cavities in the teeth than those of another city and whether differences in the technic and criteria of the examinations were distributed in the same manner as were the climatic factors. To answer this fundamental question, I have determined the closeness with which the freqencies of the various caries rates follow the distributions represented by the bell-shaped probability curve. I found that the frequency distributions of the caries rates for the age-sex groups of children in these 156 cities, followed closely the normal law of distribution, except as they may have been influenced by variables which are in themselves distributed according to the same law. The data appear, therefore, suitable for comparing the caries rate of one group with that of another. They also seem adequate for determining the correlation of the caries rates of the groups with the other variables.

The frequencies of the mean caries rates for the six age-sex groups are shown in chart 3, plotted on probability paper, as they occur $\pm \sigma$ from their means. If the points fell in a straight line, the actual distri-

6. East, B. R.: Mean Annual Hours of Sunshine and the Incidence of Dental Caries, Am. J. Pub. Health **29**:777, 1939.

7. Messner, C. T.; Gafafer, W. M.; Cady, F. C., and Dean, H. T.: Dental Survey of School Children, Ages Six to Fourteen Years, Made in 1933-1934 in Twenty-Six States, Public Health Bulletin 226, United States Treasury Department, Public Health Service, 1936.

TABLE 2.—*Distribution of 156 Cities of the United States According to Mean Caries Rates of 528,842 Children in Six Age-Sex Groups*

Boys						Girls					
Age, 6-8 Years		Age, 9-11 Years		Age, 12-14 Years		Age, 6-8 Years		Age, 9-11 Years		Age, 12-14 Years	
Caries per 100 Children	Number of Cities	Caries per 100 Children	Number of Cities	Caries per 100 Children	Number of Cities	Caries per 100 Children	Number of Cities	Caries per 100 Children	Number of Cities	Caries per 100 Children	Number of Cities
0- 24	2	0- 49	0	0- 99	0	0- 24	0	0- 49	0	0- 99	0
25- 49	11	50- 99	2	100-199	10	25- 49	9	50- 99	1	100-199	10
50- 74	23	100-149	17	200-299	26	50- 74	18	100-149	7	200-299	16
75- 99	32	150-199	25	300-399	33	75- 99	19	150-199	20	300-399	32
100-124	28	200-249	30	400-499	43	100-124	22	200-249	23	400-499	40
125-149	22	250-299	35	500-599	25	125-149	27	250-299	36	500-599	31
150-174	14	300-349	21	600-699	13	150-174	17	300-349	29	600-699	18
175-199	7	350-399	16	700-799	4	175-199	18	350-399	22	700-799	5
200-224	11	400-449	6	800 or more	2	200-224	4	400-449	11	800 or more	4
225 or more	6	450-499	3			225 or more	12	450-499	5		
		500 or more	1					500 or more	2		
Mean caries per 100 children	117.0		258.5		420.0		131.8		282.5		451.0
σ_m.....	4.1		6.9		11.6		4.1		7.2		12.4

butions would be perfectly symmetric with the "ideal" distribution of the same data. The curves follow closely the theoretic or ideal, curve of error.

The groups of girls had consistently higher mean caries rates than did boys of the same ages. This is in agreement with the results

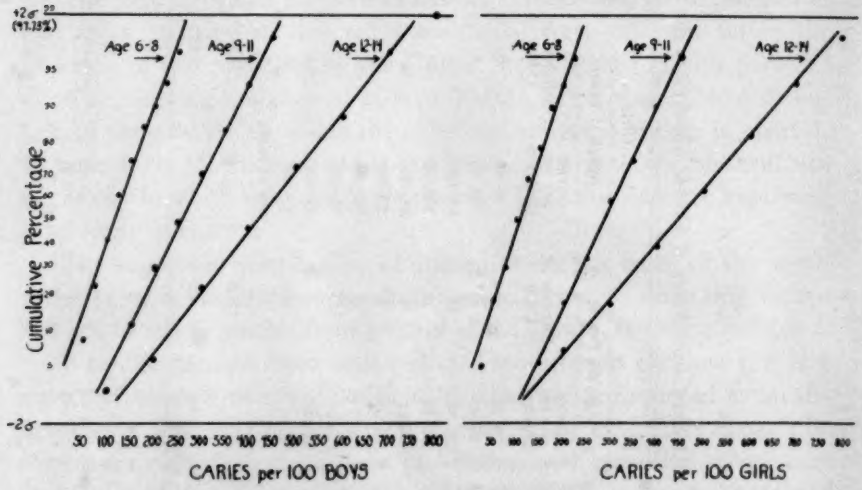

Chart 3.—Frequency distribution of mean caries rates for permanent teeth per hundred boys and per hundred girls of three age groups, plotted on probability paper.

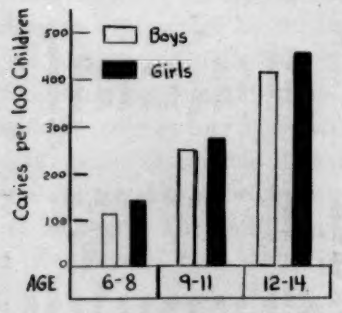

Chart 4.—Mean caries rates for permanent teeth per hundred children of six age-sex groups.

obtained in the study on rural children and also with the results of investigations of others. The mean caries rates are given in table 2 and are illustrated graphically in chart 4.

In the series there were 75 cities which had more and 81 which had less than 2,600 hours of sunshine per year. In every instance the mean caries rates for the groups of children in cities which had more than 2,600 annual hours of sunshine were lower than the rates for those in

cities which had less than that amount of sunshine. The differences between the means of the comparable age-sex groups are statistically significant. The lowest ratio between a difference and its standard error is 3.0. The probability that this difference is due to random sampling

TABLE 3.—*Relation of Mean Caries Rate for Permanent Teeth per Hundred Children and Mean Number of Hours of Sunshine per Year*

	Boys					
	Age, 6-8 Years		Age, 9-11 Years		Age, 12-14 Years	
Mean number of hours of sunshine *	>2,600	<2,600	>2,600	<2,600	>2,600	<2,600
Mean caries rate per 100 children	98.8	129.1	231.0	283.0	363.0	472.0
σm	4.9	6.6	9.5	10.1	15.1	16.8
D (m_1-m_2)	35.3 ± 8.3		52.0 ± 13.8		109.0 ± 22.6	
X/σ	4.2		3.8		4.8	
	Girls					
	Age, 6-8 Years		Age, 9-11 Years		Age, 12-14 Years	
Mean number of hours of sunshine *	>2,600	<2,600	>2,600	<2,600	>2,600	<2,600
Mean caries rate per 100 children	113.7	176.5	265.0	306.5	393.0	514.0
σm	5.3	6.9	9.3	9.8	15.8	18.4
D (m_1-m_2)	32.8 ± 8.7		41.5 ± 13.5		121.0 ± 24.3	
X/σ	3.8		3.0		5.0	

* In 75 cities the mean number of hours of sunshine per year was greater and in 81 it was less than 2,600.

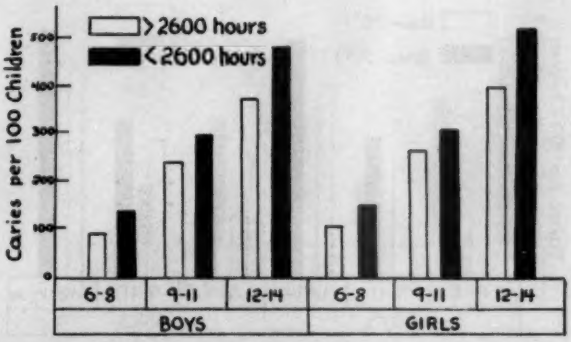

Chart 5.—Relation of mean caries rate for permanent teeth of children of six age-sex groups to number of hours of sunshine per year.

is less than 250 to 1. The relation of the mean caries rate per hundred children and the mean number of hours of sunshine per year is shown in table 3 and in chart 5.

There were 68 cities which had a mean annual winter temperature higher and 88 which had a mean annual winter temperature lower than 30 F. The mean caries rates of the various age-sex groups indicate

that the children residing where the winter temperature was higher than 30 F. had less caries than those in cities where the winter temperature was lower. The relation of mean caries rate per hundred children and mean winter temperature is shown in table 4 and in chart 6.

TABLE 4.—*Relation of Mean Caries Rate for Permanent Teeth per Hundred Children and Mean Winter Temperature*

	Boys					
	Age, 6-8 Years		Age, 9-11 Years		Age, 12-14 Years	
Mean winter (F) temperature *	>30	<30	<30	>30	>30	<30
Mean caries rate per 100 children	100.0	122.2	242.0	275.0	373.0	456.0
σm	5.0	5.3	11.3	9.4	23.5	16.2
D (m_1-m_2)	22.2 ± 7.3		33.0 ± 14.7		83.0 ± 28.5	
X/σ	3.0		2.2		2.9	
	Girls					
	Age, 6-8 Years		Age, 9-11 Years		Age, 12-14 Years	
Mean winter (F) temperature *	<30	>30	>30	<30	>30	<30
Mean caries rate per 100 children	122.8	136.9	272.0	305.0	406.0	485.0
σm	6.4	6.1	10.7	9.7	18.1	17.4
D (m_1-m_2)	14.1 ± 8.9		33.0 ± 14.4		79.0 ± 25.1	
X/σ	1.6		2.3		3.1	

* In 68 cities the mean winter temperature was higher than 30 F., and in 88 cities it was lower.

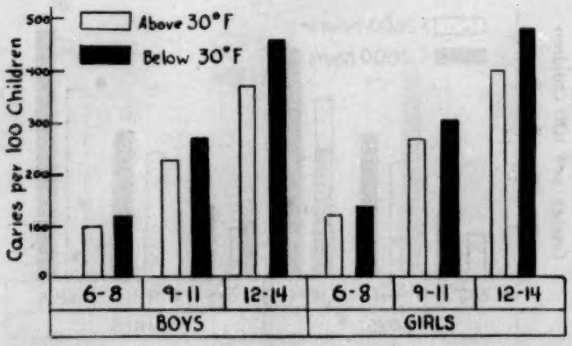

Chart 6.—Relation of mean caries rate to mean winter temperature.

There were 115 cities located north and 41 located south of latitude 40 north. In every instance the children of the southern cities had lower mean caries rates than did those of the northern cities. The lowest ratio of a standard error to its difference is 3.5. The probability that a difference of this magnitude is the result of chance is less than 2,000 to 1. In table 5 and chart 7 is shown the relation of the mean caries rate per hundred children and the latitude.

The degree of relation between the caries rates and the three environmental factors of the 156 cities was determined by computing the Pearson correlation coefficients of the various combinations. In these determinations, all the environmental class intervals, given in table 6, were employed.

TABLE 5.—*Relation of Mean Caries Rate for Permanent Teeth per Hundred Children and Latitude of Residence*

	Boys					
	Age, 6-8 Years		Age, 9-11 Years		Age, 12-14 Years	
Latitude, degrees *	<40	>40	>40	<40	>40	<40
Mean caries rate per 100 children	92.5	125.7	203.0	277.5	318.0	456.0
σm.....	7.9	5.0	13.7	7.8	23.8	13.0
D (m_1-m_2).....	33.2 ± 9.3		74.5 ± 15.8		138.0 ± 27.1	
X/σ.....	3.5		4.7		5.1	
	Girls					
	Age, 6-8 Years		Age, 9-11 Years		Age, 12-14 Years	
Latitude, degrees *	<40	>40	>40	<40	>40	<40
Mean caries rate per 100 children	101.5	141.0	234.5	311.0	350.0	487.0
σm.....	8.0	4.8	13.4	7.8	22.7	14.0
D (m_1-m_2).....	39.5 ± 9.3		76.5 ± 15.6		137.0 ± 26.6	
X/σ.....	4.2		4.9		5.2	

* Forty-one cities were south and 115 were north of latitude 40 north.

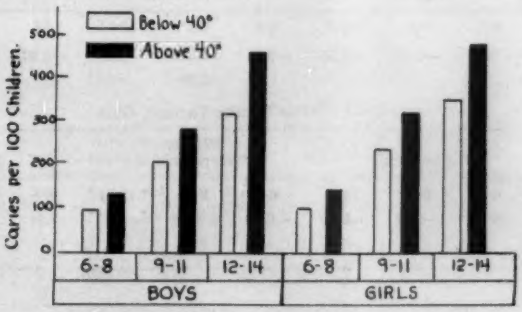

Chart 7.—Relation of mean caries rate to latitude.

All the relations are what would be expected if solar ultraviolet radiation plays a role in caries incidence. There is a negative relation between a high mean caries rate and a high number of hours of sunshine. The same relation holds for a high mean caries rate and a high mean winter temperature. There is a positive correlation between increased latitude and a high mean caries rate. Comparison of the correlation coefficients with the standard error of the series shows they are highly significant. The lowest ratio is 20. The probability that this

coefficient is due to chance is much less than 1 in 1,000,000 (table 7). However, as in our study on rural children, the coefficients do not approach unity. This should be expected because it is known that the three factors which were considered are not alone in affecting the vitamin D–producing property of sunshine. They do not operate independently in affecting the amount of ultraviolet energy which reaches the

TABLE 6.—*Class Intervals of Environmental Factors*

Sunshine (Mean Number of Yearly Hours)	Mean Winter (F.) Temperature	Latitude North
Less than 2,200	0 to 10	25 to 29
From 2,200 to 2,599	10 to 20	30 to 34
From 2,600 to 2,999	20 to 30	35 to 39
From 3,000 to 3,399	30 to 40	40 to 44
More than 3,400	40 to 50	45 to 49
	50 to 60	
	More than 60	

TABLE 7.—*Correlation Coefficients for Caries Rate for Permanent Teeth per Hundred Children and Mean Number of Annual Hours of Sunshine, Mean Winter Temperature and Latitude in 156 Cities in the United States*

	Climatic Variant, Boys								
	Sunshine			Winter Temperature			Latitude		
Age, years	6-8	9-11	12-14	6-8	9-11	12-14	6-8	9-11	12-14
r	−0.50	−0.45	−0.50	−0.34	−0.23	−0.27	−0.26	−0.40	−0.40
σ					0.08				
	Climatic Variant, Girls								
	Sunshine			Winter Temperature			Latitude		
Age, years	6-8	9-11	12-14	6-8	9-11	12-14	6-8	9-11	12-14
r	−0.49	−0.49	−0.50	−0.16	−0.28	−0.25	0.31	0.48	0.34
σ					0.08				

earth's surface. They often overlap. The correlations are, therefore, only partial correlations, and the true importance of the environmental factors in the problem cannot be determined by this statistical method.

The partial regression equation of Fisher [8] was employed, as in the study of rural children, to measure better the relation between any one of the three factors in the problem exclusive of the remaining two. In computing the partial regression coefficients, the correlation coefficients

8. Fisher, R. A.: Statistical Methods for Research Workers, London, Oliver & Boyd, 1936.

of the three possible combinations of environmental or independent variables were determined. The values are given in table 8.

The partial regression equation for the study on city children has the form: $c = C - S(s-2{,}602.5) - T(t-29.5) + L(1-41.3)$, in which c = mean caries rate for permanent teeth in any age-sex group in any city, C the mean caries rate for the same age-sex group in 156 cities,

TABLE 8.—*Correlation Coefficients for Mean Number of Annual Hours of Sunshine, Mean Winter Temperature and Latitude in 156 Cities of the United States*

Environmental Combination	Sunshine and Latitude	Sunshine and Winter Temperature	Latitude and Winter Temperature
r	−0.49	±0.39	−0.96
σ		0.08	

TABLE 9.—*Partial Regression Coefficients for the Mean Caries Rate for Permanent Teeth per Hundred Children and the Mean Number of Annual Hours of Sunshine, Mean Winter Temperature and Latitude in 156 Cities of the United States*

	Climatic Variant, Boys								
	Add 100 Hours of Sunshine per Year			Add 10 F. to Mean Winter Temperature			Add 1 Degree to Latitude		
Age, years	6-8	9-11	12-14	6-8	9-11	12-14	6-8	9-11	12-14
Partial regression coefficient	−6.9	−4.0	−15.0	−20.0	−90.0	−70.0	6.0	32.0	29.8
σ	1.7	1.7	4.5	14.7	15.5	38.0	4.6	5.0	12.0
X/σ	4.0	2.8	3.3	1.4	5.8	1.8	1.3	6.4	2.5
	Climatic Variant, Girls								
	Add 100 Hours of Sunshine per Year			Add 10 F. to Mean Winter Temperature			Add 1 Degree to Latitude		
Age, years	6-8	9-11	12-14	6-8	9-11	12-14	6-8	9-11	12-14
Partial regression coefficient	−5.0	−6.0	−19.5	−43.5	−72.0	−20.0	14.3	27.1	63.0
σ	1.6	2.6	5.2	25.0	23.0	47.0	4.4	7.1	73.0
X/σ	3.0	2.3	3.7	1.7	3.1	0.4	3.3	3.8	0.8

s, t and 1 mean number of hours of sunshine per year, mean winter temperature and latitude of the city, S, T and L the corresponding partial regression coefficients computed to yield the best mathematical fit to all the data, 2,602.5 the mean number of hours of sunshine per year of 156 cities, 29.5 the mean annual winter temperature of 156 cities and 41.3 the mean latitude of 156 cities.

In table 9 appear the partial regression coefficients of the caries rates for the permanent teeth of the various age-sex groups and the environmental factors. These coefficients are given for the influences

on the caries rates for the permanent teeth of changes in the three environmental factors. The percentage change from the mean caries rates for the various age-sex groups associated with the various independent variables are given in table 10. In computing these values, all

TABLE 10.—*Effect on the Mean Caries Rate for Permanent Teeth per Hundred Children in 156 Cities of the United States, of Changes in Number of Annual Hours of Sunshine, Mean Winter Temperature and Latitude*

	Climatic Variant, Boys								
	Add 100 Hours of Sunshine per Year			Add 10 F. to Mean Winter Temperature			Add 1 Degree to Latitude		
Age, years	6-8	9-11	12-14	6-8	9-11	12-14	6-8	9-11	12-14
Percentage change from mean caries rate	—5.9	—1.6	—3.6	—17.1	—35.0	—16.7	5.1	12.4	7.1
σ	1.4	0.7	1.1	12.2	6.0	9.3	3.9	1.9	2.8
X/σ	4.0	2.3	3.3	1.4	5.8	1.8	1.3	6.4	2.5
	Climatic Variant, Girls								
	Add 100 Hours of Sunshine per Year			Add 10 F. to Mean Winter Temperature			Add 1 Degree to Latitude		
Age, years	6-8	9-11	12-14	6-8	9-11	12-14	6-8	9-11	12-14
Percentage change from mean caries rate	—3.8	—2.1	—4.3	—33.0	—25.5	—4.4	10.9	9.6	14.0
σ	1.3	0.9	1.2	19.4	8.2	11.0	3.3	2.5	17.5
X/σ	3.0	2.3	3.7	1.7	3.1	0.4	3.3	3.8	0.8

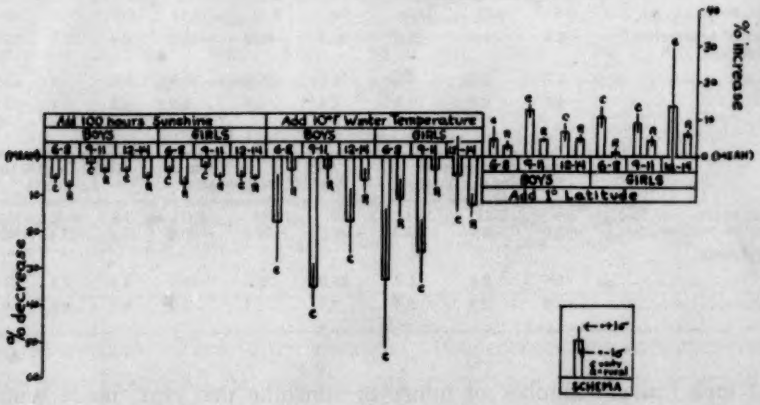

Chart 8.—Effect on mean caries rate for permanent teeth of changes in the number of hours of sunshine per year, in the mean winter temperature and in the latitude in six age-sex groups of rural children and six comparable groups of city children.

the class intervals of the environmental factors and the caries rates given in tables 6 and 2 were taken into consideration. The percentage relationships are shown graphically in chart 8. The corresponding percentage relationships for rural children, previously reported, are also shown.

The results from the study on city children are consistent with those of the study on rural children. They also are consistent with my thesis that environmental conditions which favor the exposure to solar ultraviolet energy are related to a greater resistance to dental caries in children.

The addition of 100 hours of sunshine per year to the mean number of hours of sunshine per year in the rural and the semirural counties was associated with a percentage decrease in the mean caries rate of 5.5, if the figures for the three age groups of boys were combined and averaged. For the city boys the average percentage decrease associated with such a change in hours of sunshine was only 3.7. Approximately the same difference exists in the figures for the city and the rural girls.

A drop in winter temperature of 10 degrees (F.) was related to a much greater increase in the mean caries rates of the groups of city children than in the rates of the groups of rural children. The average increase in the rates for the three age groups of city boys was five and six-tenths times that in the rates for the rural boys. For the city girls the change was twice as great as for the country girls.

Latitude has a more profound influence in cities than in the more rural localities. The increase in caries rates of city boys was twice that of the increase in the rates of rural boys when the latitude was increased. The increase in caries rates of city girls was three times as great as the increase in the rates of country girls.

In the paper concerning rural children, evidence was presented on the relation of hours of sunshine and latitude to the total amount of ultraviolet energy at a given point on the earth's surface. It has been demonstrated that the caries rates of both city and rural children are in agreement with the climatic conditions which make for greater or for less ultraviolet energy at their place of residence. The greater the amount of ultraviolet, the lower is the caries rate. The milder the climate, the lower is the caries rate.

Why is there this difference in response between rural and city children when the same amount of sunshine and the same temperature and latitude prevail at city and at rural location? Are these variations in agreement with my hypothesis? And have observations been made which establish that when the amount of sunshine, the mean winter temperature and the mean latitude are the same in a city and at a more rural point, more solar ultraviolet energy reaches the earth's surface at the country than at the city location?

The values for the rural and the city children differ only in magnitude. I believe that the differences are important collateral evidence in support of my hypothesis.

It is general knowledge that pollution of the air by smoke is greater over cities than over rural areas. Numerous papers have established this. I wish to comment on two publications which demonstrate that the contamination of air does take place and that the pollution decreases the amount of solar ultraviolet radiation which reaches the street level. Shrader and his associates,[9] of the Baltimore health department, made measurements of the pollution of air in that city. They also measured the ultraviolet energy at different points in the city and its suburbs. They collected at the city hall, the city's center, a total of 18 tons (18,288 Kg.) of solids per square mile (2.59 square kilometers) per year from the air. In the suburbs, 3 miles (4.8 kilometers) from the city hall, the amount collected was 9 tons (9,144 Kg.), while on farms, 10 miles (16.09 kilometers) from the city hall, the amount was only 3½ tons (3,556 Kg.) per square mile per year. At Baltimore, the pollution of the air by smoke and from other sources was inversely proportional to the distance from the center of the city. These investigators also made

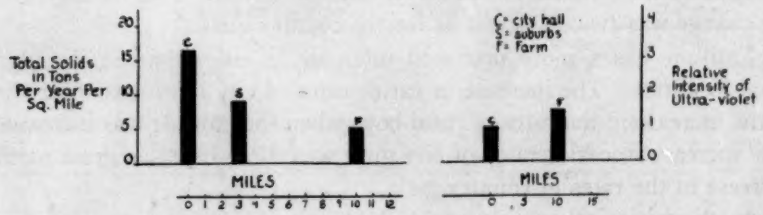

Chart 9.—Relation of air pollution to intensity of ultraviolet radiation in and about Baltimore. (Data are from the study of Shrader and his associates.[9])

measurements of the solar ultraviolet radiation at the city hall and at the farms 10 miles away. There was one and a half times as much ultraviolet energy at the farms as at the city hall. In chart 9 the data of Shrader are shown graphically.

Tonney and his associates,[10] of the Chicago Department of Health, carried on extensive investigations in Chicago similar to those made in Baltimore. They measured the ultraviolet radiation in the "Loop," the center of congestion in Chicago, and at points in the city's suburbs. During December, January and February there was two and three-tenths times as much ultraviolet energy at the "clear point" in the suburbs as in the congested "Loop" district. They also measured the relative amounts of ultraviolet energy during the various hours of a

9. Shrader, J. H.; Coblentz, M. H., and Korff, F. A.: Effect of Atmospheric Pollution upon Incidence of Solar Ultraviolet Light, Am. J. Pub. Health **19**:717, 1929.

10. Tonney, F. O.; Hoeft, G. L., and Somers, P. P.: Loss of Actinic Intensity in Urban Sunshine Due to Air Pollution. J. Prev. Med. **4**:139, 1930.

winter day at the smoky, congested center and in the suburbs. The differences are striking and significant. They also made hourly observations during a July day in the "Loop" district and simultaneously at a rural point, 33 miles (53.09 kilometers) away. Their data demonstrate that even in summer, when furnaces are not in operation for heating dwellings and offices, sufficient pollution of air occurs over a city to reduce appreciably the vitamin D–producing property of the sunshine. The amount of sunshine reaching the city was reduced as much as 50 per cent as compared with that which reached the earth at the rural location. Some of Tonney's data are in chart 10.

Ives, Britten, Armstrong, Gill and Goldman,[11] of the United States Public Health Service, made extensive investigations on the pollution of the air in cities of the United States. They found that the greatest amounts of solids accumulated in the air over the cities during the

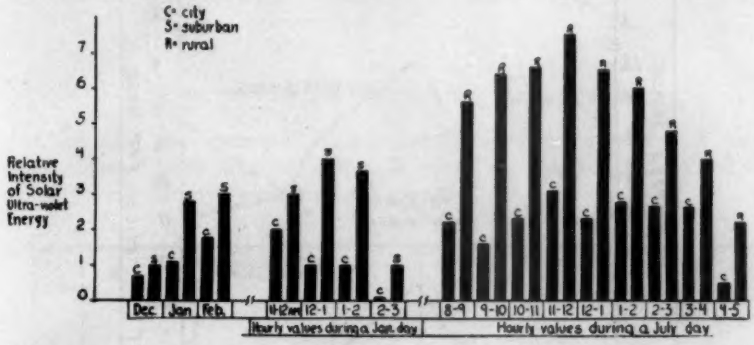

Chart 10.—Relation of intensity of ultraviolet radiation in and about Chicago to season and to hour of the day. (Data are from the study of Tonney and his associates.[10])

coldest months. In winter the pollution was twice that in the summer. The curves of Ives and his associates demonstrating the relation of the pollution of the air to the temperature and the month of the year are reproduced in chart 11. The pollution of the air represented as average "shade."[12] It will be noted that in *A* of chart 11 the air pollution curve for the months of the year follows closely the temperature curve except from January to May.[13] An explanation for this diversion

11. Ives, J. E.; Britten, R. H.; Armstrong, D. W.; Gill, W. A., and Goldman, F. H.: Atmospheric Pollution of American Cities for the Years 1931-1933, with Special Reference to Solid Constituents of Pollution, Public Health Bulletin 224, United States Treasury Department, Public Health Service, 1936.

12. "Shade" refers to the discoloration of a filter by the passage of known amounts of air through it under controlled conditions.

13. It should be noted that the temperature curve is inverted.

appears in the other curves. It is known that when the wind velocity doubles, the pollution of the air is decreased six tenths. In *B* of chart 11 the curves for air pollution and wind velocity of the 14 cities are seen to be dissimilar except during October and November. Comparison of a curve based on the product of temperature and wind velocity with the curve for air pollution shows that they are closely related.

In chart 12 the "estimated normal seasonal pollution curve" of Ives and his associates has been reproduced.

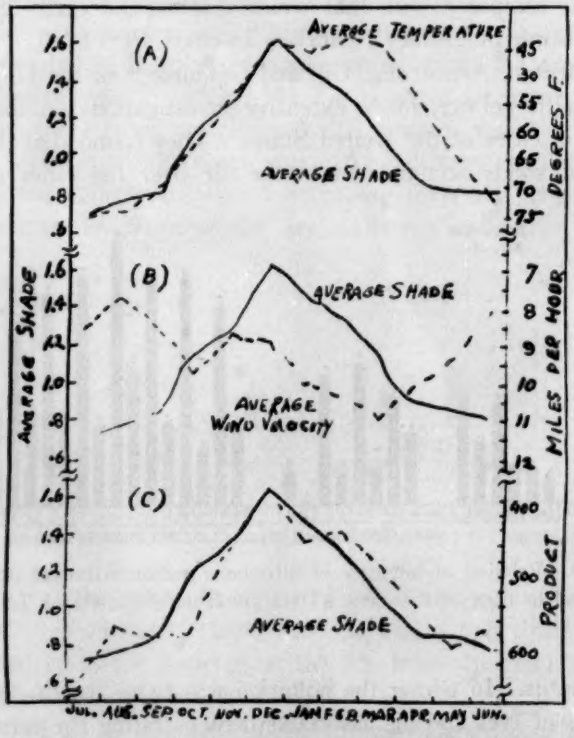

Chart 11.—Relation of air pollution ("average shade") curve for 14 cities of the United States (*A*) to average temperature curve, (*B*) to average wind velocity curve and (*C*) to a curve based on the product of temperature and wind velocity (from Ives and others [11]).

Ives and his associates also studied the effect of an overcast sky on the pollution of air. They found that during the hours of the day when children could be exposed to the sunshine, pollution of the air was about twice as great on cloudy as on clear days. This was thought to be due in large measure to the curtailment of ascending currents of air on cloudy days. In chart 13 are reproduced these air pollution curves for cloudy and for clear days. The readings are given for each hour of two consecutive days.

Thus it appears that the colder the day, the greater is the pollution of the air. The greater the pollution of the air, the less is the solar ultraviolet energy available at the earth's surface to create vitamin D in a child's skin. It is also apparently true that the cloudier the day, the greater is the pollution of the air. I have previously shown that

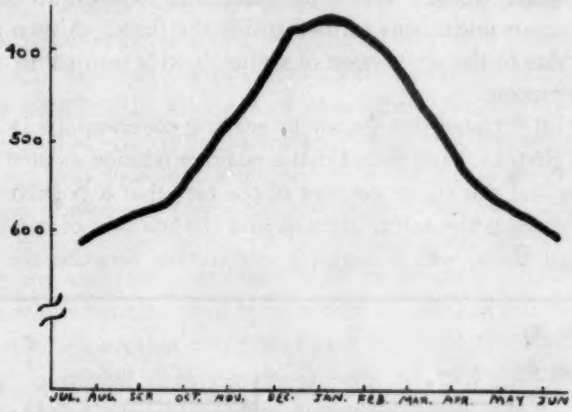

Chart 12.—The "estimated normal seasonal air pollution curve" of American cities, obtained by plotting the product of normal monthly temperature and normal monthly wind velocity (from Ives and others [11]).

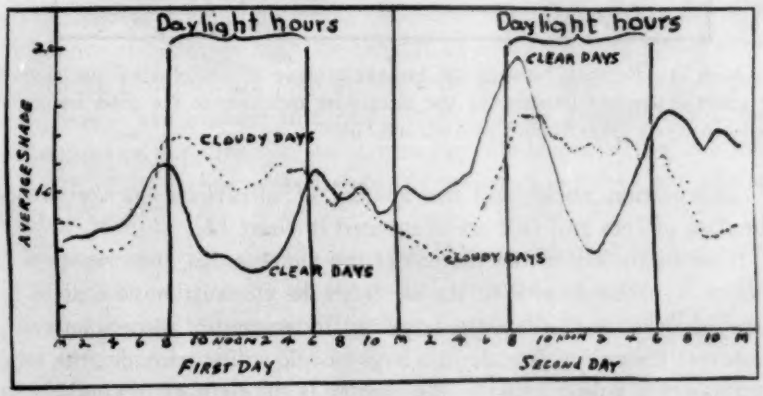

Chart 13.—Air pollution in 14 cities of the United States on clear and on cloudy days (from Ives and others [11]).

there is less ultraviolet energy available on cloudy than on clear days. The combination of cold and cloudy weather seems to reduce greatly the amount of ultraviolet energy available. This effect is much more noticeable in cities than in rural areas.

But there are other conditions which might have a bearing on the fact that the effect on caries incidence of the climatic variables considered in this study is more pronounced in the city than in the country.

In 1912 Aitkin [14] suggested that sunlight could, under certain conditions, produce fog. He noted that fog was more apt to appear when the air was smoky. He attributed this to the action of the ultraviolet energy of sunlight on the sulfur dioxide present in the air from the combustion of coal in furnaces. He confined a mixture of air and sulfur dioxide in a quartz flask. When the flask was exposed to ultraviolet light, condensation nuclei was formed inside the flask. Aitken assumed that this was due to the conversion of sulfur dioxide into sulfur trioxide, which is hygroscopic.

Ives and Gill [15] tested this theory by making observations in 15 cities of the United States. They found that a positive relation existed between the smokiness and the sulfur content of the air; that a positive correlation existed between the sulfur content and the number of condensation nuclei and that there was a negative correlation between the number

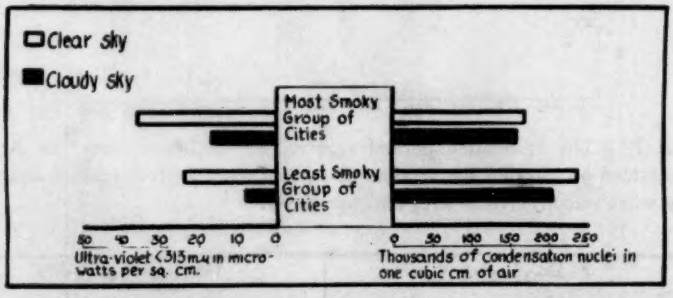
Clear sky
Cloudy sky
Most Smoky Group of Cities
Least Smoky Group of Cities
50 40 30 20 10 0
Ultra-violet <313mμ in micro-watts per sq. cm.
0 50 100 150 200 250
Thousands of condensation nuclei in one cubic cm. of air

Chart 14.—Relation between the average number of condensation nuclei in the air and the average intensity of the ultraviolet radiation in the most smoky and the least smoky cities studied by Ives and Gill.[15]

of condensation nuclei and the amount of ultraviolet energy present. The data of Ives and Gill are illustrated in chart 14.

It seems to follow that the colder the temperature, the greater is the amount of sulfur dioxide in the air from the combustion of coal in furnaces; the clearer the day, the larger is the amount of ultraviolet energy to convert the sulfur dioxide into hygroscopic sulfur trioxide; the larger the amount of sulfur trioxide, the greater is the number of condensation nuclei; the greater the number of condensation nuclei, the denser are the haze and fog over the city; the denser the fog, the greater is the depletion of solar ultraviolet energy; the greater the depletion of ultraviolet energy,

14. Aitken, J.: The Sun as a Fog Producer, Proc. Roy. Soc. Edinburgh **32**: 183-215, 1911-1912.

15. Ives, J. E., and Gill, W. A.: Measurements of Ultraviolet Solar Radiation and Illumination in American Cities During the Years 1931 to 1933, Public Health Bulletin 233, United States Treasury Department, Public Health Service, 1936.

the less is the opportunity for production of vitamin D in the child's body. The conditions just described are more apparent in cities than in smaller communities.

Coblentz and his associates,[16] of the United States Bureau of Standards, have demonstrated that snow reflects as much as from 50 to 100 per cent of the ultraviolet rays of sunlight. During the winter months this could be an important factor in the amount of vitamin D produced in the skin of children. This offers another basis for the existence of a difference between the amounts of ultarviolet energy available to rural and to city children. It is undoubtedly true that the removal of snow from streets and walks is more general in the city than in the country. A great portion of city pavements are of dark material, which is a poor reflector of ultraviolet light. In large cities great facility is shown in removing snow almost completely from pavements. In the rural areas snow generally remains until it is melted by the sun's heat. One other factor in this connection could also play a role in the problem. In the cities the snow that does remain is soon covered with soot from the chimneys. And the colder the climate and the larger the city, the greater is the tendency for solids from forced firing to foul the snow's reflecting surface.

Latitude had a more profound effect on caries incidence among city than among rural children. This can result, in part at least, from the interference of buildings with the passage of direct sunlight to the street. In cities the buildings are both higher and closer together than in more rural areas. The amount of direct sunlight which reaches city streets is dependent on the direction the streets run, the height of the buildings, the width of the street and the amount of space between the various buildings.

It is also a mathematically demonstrable fact that given a constant height of buildings, width of street and direction of street, the more northerly the city, the greater is the street surface which will not receive direct sunlight.

It can be demonstrated that the surface of streets which run east and west, in latitudes which are considered in this study, receive little direct sunshine. In New York city, for example, a large percentage of the population reside in areas where the dwellings are not only several stories in height but where each block presents a solid front.

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16. Coblentz, W. W.; Stair, R., and Hogue, J. M.: Measurements of Ultraviolet Solar Radiation in Various Localities, J. Research **11**:133, 1933. Coblentz, W. W., and Stair, R.: Factors Affecting Ultraviolet Solar-Radiation Intensities, ibid. **15**:123, 1935.

Atkinson [17] has made a careful study of "orientation of buildings, or planning for sunlight." In chart 15 are diagrams [18] which illustrate the combined effect of the height of the buildings, the width of the street and the diurnal and seasonal position of the sun on the possibility that a child will be directly exposed to solar ultraviolet rays while in the street. The diagrams show that at latitude 42 north the surface of a street which runs east and west would receive no direct sunlight during the winter solstice.[19] It is only during the summer solstice that the entire street surface could receive direct sunlight, and this could occur only after 4 p. m. During the winter the ultraviolet energy is weak because of the increased thickness of the air mass through which the

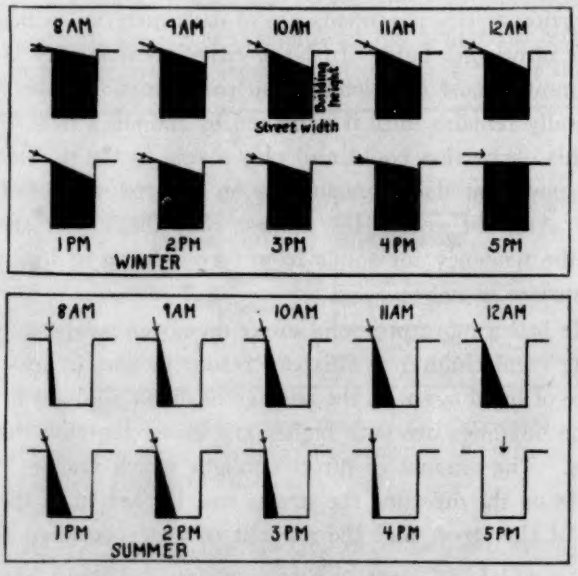

Chart 15.—Diagrams illustrating the effect on the amount of ultraviolet radiation which reaches the street of the height of the buildings, the width of the street and the diurnal and seasonal position of the sun. (The diagrams were suggested by the work of Atkinson.[17])

sun's rays must pass to reach the earth's surface. The sun's rays are depleted of their vitamin D–producing property, which is closely related to the diurnal position of the sun, by 4 p. m. These conditions and variations from them could account, at least in part, for the greater effectiveness of latitude in increasing the susceptibility of city than of rural children to caries.

17. Atkinson, W.: The Orientation of Buildings, or Planning for Sunlight, New York, John Wiley & Sons, 1912.

18. The diagrams were suggested by the work of Atkinson,[17] pp. 111-113.

19. The latitude of Columbia University, in New York city, is 40° 48′ 35″, and that of the observatory at the University of Chicago is 41° 50′ 1″.

The foregoing evidence indicates that conditions which are known to exist in cities reduce the solar ultraviolet energy to a greater degree than at rural points, when the temperature, the amount of sunshine and the latitude of the two locations are identical. The caries rates of city children are higher than those of children of corresponding age and sex residing in rural areas. The high caries rates have a positive correlation with the conditions which are known to interfere with the exposure of the children's skins to vitamin D–producing solar energy. The greater the opportunity for creation of vitamin D in the body, the greater is the resistance of the teeth to decay.

I have shown that the greatest pollution of air occurs in the centers of cities. It seems reasonable to assume that the larger the city, the greater is the area which has marked pollution of air. I have also

TABLE 11.—*Mean Caries Rates per Hundred Children in Cities of Three Sizes in the United States*

	Boys								
Population of city.....	10,000-24,999			25,000-99,999			Over 100,000		
Age of children, years...	6-8	9-11	12-14	6-8	9-11	12-14	6-8	9-11	12-14
Mean caries rate per 100 children	107.6	242.5	400.0	117.5	252.5	419.0	123.4	278.5	443.0
σ.....	8.9	14.4	23.0	7.0	12.8	21.3	6.3	10.0	17.6
	Girls								
Population of city.....	10,000-24,999			25,000-99,999			Over 100,000		
Age of children, years...	6-8	9-11	12-14	6-8	9-11	12-14	6-8	9-11	12-14
Mean caries rate per 100 children	119.7	263.0	428.0	130.7	280.5	450.0	138.0	306.5	475.0
σ.....	7.9	14.0	24.4	7.4	10.7	22.2	6.2	10.6	20.8

called attention to the fact that the larger the city, the taller are the buildings in relation to the width of the street. Dwellings are usually closer together in the larger cities. The larger the city, the greater is the facility in removing the snow, which reflects the ultraviolet rays, from streets and walks. The larger the city, the greater is the amount of solids from the combustion of coal to foul the reflecting surface of that snow which is allowed to remain. These circumstances lead to the hypothesis that a positive correlation exists between the mean caries rates in children and the size of the city in which they live.

Of the 156 cities in this study, the population of 55 is over 100,000, that of 55 is between 25,000 and 99,999 and that of the remaining 44 is less than 25,000 but more than 10,000. I have computed the mean caries rates for the cities according to their size. The values and their respective standard errors are given in table 11. The results support the hypothesis. The larger the city, the higher is the mean caries rate. When the difference between any two successive means of the same age

and sex group is compared with its standard error, the value cannot be said to be statistically significant. However, when the series is considered as a whole, the consistency is impressive.

I computed the correlation coefficients of the mean caries rates of the various age-sex groups with the size of the cities. There is a positive correlation in every case. The coefficients, from comparison with their standard errors, are seen to be highly significant. The smallest ratio between a value and its standard error is 4.9. The probability that this value is traceable to chance or to random sampling is too remote to consider seriously. The coefficients and their standard errors are given in table 12.

TABLE 12.—*Correlation Ratio Between Size* of City and Mean Caries Rate per Hundred Children*

	Boys			Girls		
Age of children, years.....	6-8	9-11	12-14	6-8	9-11	12-14
r.....	0.39	0.60	0.39	0.49	0.55	0.43
σ.....			0.08			

* The population of 46 cities was between 10,000 and 24,999, that of 55 was between 25,000 and 99,999 and that of 55 was more than 100,000.

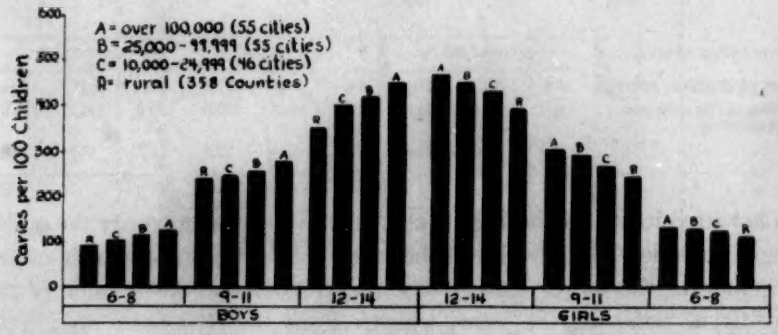

Chart 16.—Mean caries rates for permanent teeth for six age-sex groups of rural children and for comparable groups in cities of three sizes.

In chart 16 the mean caries rates of the various groups, based on the size of the city, of residence, are presented graphically. The various mean caries values for the rural children have been included to illustrate further the association of caries with congestion of population. This extends the consistency and lends further validity to the thesis that the more unfavorable the conditions for the exposure of children's skins to the vitamin D–producing properties of sunshine, the higher is their dental caries rate.

SUMMARY

I have presented further evidence that the amount of solar ultraviolet energy available at a given point on the earth's surface is related to the amount of dental decay in the teeth of children residing at that location.

The more favorable the conditions are for the exposure of children's skins to the vitamin D–producing rays of the sun, the less is the dental decay.

The results of this study lend further validity to the reports that the caries incidence in children is lowered when they are regularly fed vitamin D. They give particular support to the report that the administration to children of graded amounts of vitamin D from a natural (animal) source, such as vitamin D milk, resulted in graded caries prevention.

The larger the city and the more northerly its location, the greater is the need for the administration of vitamin D to promote resistance to caries in children residing in that city.

Children in southern cities have less caries than those in the north. However, the evidence indicates that even in the southern cities included in this study children do not obtain from the sun or from their food sufficient vitamin D for optimum resistance to caries.

These results support the soundness of the recommendation by the Health Organization of the League of Nations that public health authorities should give the "closest attention" to the possibility of decreasing the incidence of dental caries by the administration of vitamin D to children.

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ATTEMPTS TO SENSITIZE MONKEYS TO SCARLET FEVER ANTITOXIN

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Kopeloff and his associates[1] gave many injections of normal horse serum or egg white to Macacus rhesus monkeys. These investigators found that their blood serums contained precipitins and that the animals had become sensitized, since they could be shocked to death by subsequent injections of the specific antigen.

Recently, a report was made of the results of the clinical use of horse serum scarlet fever antitoxin from which the factor causing serum sickness had been removed.[2] If monkeys sensitized to normal horse serum according to the methods of Kopeloff and his co-workers are given injections of this type of scarlet fever antitoxin, which lacks the factor causing serum reactions in man, they should have no reactions.

METHODS AND MATERIALS

The plan of the work reported on here was to give monkeys injections either of concentrated scarlet fever antitoxin or of normal horse serum until sensitization occurred, that is, until the precipitin titer of the blood serum was sufficiently high, the reaction to the cutaneous test was positive and the symptoms of shock had appeared, and, while they were in that state, to determine if they were sensitive to either normal horse serum or scarlet fever antitoxin.

The animals used in these experiments were Macaca mulatta monkeys in excellent health and weighing approximately 1,900 to 3,000 Gm. Although a few of the animals had been used previously in experiments with poliomyelitis virus, they had remained normal, and several months had elapsed since they had been used.

From the Division of Contagious Diseases and the Department of Medicine, City Hospital, and the Department of Pediatrics, Western Reserve University.

1. Kopeloff, L. M., and Kopeloff, N.: Anaphylaxis in Rhesus Monkeys: I. Horse Serum as Antigen, J. Immunol. **36**:83-99 (Feb.) 1939; II. Egg-White as Antigen, ibid. **36**:101-127 (Feb.) 1939. Davidoff, L. M.; Kopeloff, N., and Kopeloff, L. M.: Anaphylaxis in Decerebrated Monkeys, J. Lab. & Clin. Med. **23**:30-32 (Oct.) 1937.

2. Toomey, J. A., and Baker, C. S.: Treatment of Scarlet Fever with Specific Antitoxins of Low Protein Content, J. Pediat. **12**:439-448 (April) 1938. Toomey, J. A., and Kimball, E. R., Jr.: Treatment of Scarlet Fever with Specific Antitoxin of Low Protein Content: II, ibid. **15**:238-244 (Aug.) 1939.

The method of testing for precipitins was as follows: Into each of five test tubes was put 0.1 cc. of undiluted monkey serum; 0.1 cc. of antigen in dilutions of 1:1, 1:10, 1:100, 1:1,000 and 1:10,000, respectively, was then put in a layer over the serum in each tube. The tubes were placed in the incubator for one hour; readings were made at the end of twenty minutes, one hour and twenty-four hours. The usual white ring at the juxtaposition of the liquids denoted a positive reaction. The antibody-antigen combinations were reversed in their proportions, with no different effect. All animals were tested cutaneously each time before any antigen was used by injecting 0.01 to 0.02 cc. of the antigen intradermally. Readings were made five and thirty minutes later.

RESULTS

EXPERIMENT 1.—Each of 5 animals was given an intravenous injection of 1 per cent of its body weight of scarlet fever antitoxin[3] diluted 1:10 with a physiologic solution of sodium chloride. Thirteen such injections were given between March 22 and Dec. 17, 1939. Each injection consisted of at least two-thirds to one human therapeutic dose. The antitoxins used were obtained before January 1940, at which time the Scarlet Fever Committee changed the number of units in the package of scarlet fever antitoxin.

Not one of the injections caused a systemic reaction; the precipitin titers produced were negligible, and no reaction to a cutaneous test was found to be positive.

Thus, these animals did not become sensitized to scarlet fever antitoxin, for even with the amounts used not only was there an absence of serum reactions as well as precipitins but the reaction to the cutaneous test was always negative. The intervals between injections were varied without any effect on sensitization.

If a man weighing 50 Kg. was given comparable doses of antitoxin, he would receive thirteen injections, each of 50 cc. of antitoxin in 500 cc. of physiologic solution of sodium chloride, or a total of 650 cc. of antitoxin in 6,500 cc. of physiologic solution of sodium chloride.

Despite the fact that no signs of sensitization occurred, the animals were given injections of normal horse serum with no effect (table 1).

It was concluded, therefore, that this antigen failed to sensitize these animals.

EXPERIMENT 2.—This experiment was similar to the first one, the only differences being that another brand[4] of scarlet fever antitoxin was used and that the doses were much larger. Five cubic centimeters of scarlet fever antitoxin in an amount of physiologic solution of sodium chloride equivalent to 1 per cent of the body weight (except as indicated) was injected intravenously each time. This amount of antitoxin was one and two-thirds times as large as the average therapeutic dose for man. Eighteen injections were given to each of 3 monkeys, a total of 90 cc. of scarlet fever antitoxin to each animal. This amount roughly corresponds to thirty of the therapeutic injections given to man. The intervals between injections varied, short or long as the case might be. Toward the end of the experiment, the antitoxin was given undiluted with the same results; that is, the reactions to the cutaneous test did not become positive, there were no systemic reactions and no precipitins were formed (table 2).

Thus, this antitoxin also failed to sensitize these animals.

3. The serum used was prepared by Parke, Davis & Co., Detroit.

4. The serum used was prepared by Lederle Laboratories, Inc., Pearl River, N. Y.

TABLE 1.—*Results of Attempts to Sensitize Monkeys by Intravenous Administration of Scarlet Fever Antitoxin* *

Monkey	Weight, Gm.	Amount of Antitoxin, Cc. of 1:10 Dilution	Results †	Dose 1 3/22/39	Dose 2 3/29/39	Dose 3 4/5/39	Dose 4 4/12/39	Dose 5 4/19/39	Dose 6 5/10/39	Dose 7 5/24/39	Dose 8 6/7/39	Dose 9 6/28/39	Dose 10 7/12/39	Dose 11 8/9/39	Dose 12 10/11/39	Dose 13 11/17/39	Dose 14 12/17/39	Dose 15 12/17/39
1772	1,060	19.6	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			R	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			P	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1767	2,445	25.4	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			R	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			P	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1915	2,200	22.0	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			R	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			P	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1929	2,515	25.1	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			R	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			P	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1906	3,050	30.5	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			R	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			P	1:100	0	0	0	0	0	0	0	0	0	0	0	0	0	0

* The scarlet fever antitoxin used was manufactured by Parke, Davis & Co.
† In this and in subsequent tables S = reaction to the cutaneous test, R = systemic reaction and P = precipitins.

TABLE 2.—*Results of Attempts to Sensitize Monkeys by Intravenous Administration of Scarlet Fever Antitoxin* *

Monkey	Weight, Gm.	Amount of Antitoxin, Cc. of Serum in Cc. of Physiologic Solution of Sodium Chloride	Results	Dose 1 Oct. 23	2 Oct. 27	3 Oct. 31	4 Nov. 4	5 Nov. 8	6 Nov. 12	7 Nov. 16	8 Nov. 20	9 Nov. 24	10 Nov. 28	11 Dec. 11	12 Dec. 15	13 Dec. 19	14 Dec. 23	15 Dec. 27	16† Jan. 27	17† Feb. 27	18† March 27
				Date, 1939															Date, 1940		
2158	2,361	5 in 23.6	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			R	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			P	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2159	2,970	5 in 29.7	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			R	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			P	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2160	3,290	5 in 32.9	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			R	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			P	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

* The scarlet fever antitoxin was manufactured by Lederle Laboratories, Inc.
† The dose was 5 cc. of undiluted antitoxin.

TABLE 3.—*Results of Attempts to Sensitize Monkeys by Intravenous Administration of Normal Horse Serum and Scarlet Fever Antitoxin*

Monkey	Weight, Gm.	Amount of Undiluted Material, Cc.	Material* and Results	Dose 1 March 22, 1939	Dose 2 March 29, 1939	Dose 3 April 5, 1939	Dose 4 April 12, 1939	Dose 5 April 19, 1939	Dose 6 May 10, 1939	Dose 7 May 24, 1939	Dose 8 June 7, 1939	Dose 9 June 28, 1939	Dose 10 July 12, 1939	Dose 11 Aug. 9, 1939	Dose 12 Oct. 11, 1939	Dose 13 Nov. 17, 1939	Dose 14 Dec. 17, 1939	Dose 15 Jan. 17, 1940
1763	2,920	29.2	M	NHS	NHS	NHS	NHS	NHS	NHS	NHS	NHS	NHS	NHS	NHS	SFA	NHS	SFA	NHS
			S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			R	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			P	0	0	1:100	1:100	1:1,000	1:1,000	1:10	0	0	0	0	0	0	0	0
1774	3,050	30.5	M	NHS	NHS	NHS	NHS	NHS	Died									
			S	0	0	0	0	0										
			R	0	0	0	0	Shocked										
			P	1:10,000	1:10	1:100	1:1,000	1:1,000										
1910	2,040	20.4	M	NHS	NHS	NHS	NHS	NHS	SFA	NHS	SFA	NHS	SFA	NHS	NHS	SFA	NHS	SFA
			S	0	0	0	0	0	Positive to NHS and SFA	0	0	0	0	0	0	0	0	0
			R	0	0	0	0	Cyanosis, hemoptysis, inactivity	Cyanosis, tremors, tachycardia	0	Chill	Chill	Chill	0	0	0	0	0
			P	1:40	0	0	1:100	1:10,000	1:1,000	1:1,000	1:10,000	1:10,000	1:100	1:100	0	1:100	0	0
1776	2,690	26.9	M	NHS	NHS	NHS	NHS	NHS	SFA	NHS								
			S	0	0	0	0	0	Negative to NHS and SFA	0								
			R	Dyspnea	0	0	0	Asthmatic breathing	Restlessness, hyperpnea	Shocked, died								
			P	1:100	1:10	1:100	1:100	1:1,000	1:1,000	1:1,000								
1733	2,370	23.7	M	NHS	NHS	NHS	NHS	NHS	NHS	NHS	NHS	NHS	NHS	NHS	SFA	NHS	SFA	NHS
			S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			R	0	Cyanosis, dyspnea, restlessness	0	0	0	0	0	0	0	0	0	0	0	0	0
			P	1:10	1:100	1:100	1:10	1:100	1:100	1:100	1:10	1:10	0	0	0	0	0	0

* M signifies material, NHS = normal horse serum and SFA = scarlet fever antitoxin.

EXPERIMENT 3.—Simultaneously with experiment 1, 5 other animals were given injections of normal horse serum in amounts equivalent to 1 per cent of their body weights, as noted in table 3. The purpose was to render them sensitive to horse serum and then to inject purified scarlet fever antitoxin. If the animals reacted, it might then be inferred that purification had not removed all the sensitizing factors from the horse serum, as has been claimed; if they did not react, it might be concluded that the sensitizing factors had been removed. The disappointing results of this experiment were as follows:

Animal 1763 was given thirteen injections of horse serum and two of scarlet fever antitoxin but remained asymptomatic from March 22, 1939, to Jan. 17, 1940, when the injections were discontinued. Neither a systemic reaction nor a positive reaction to the cutaneous test developed, and the precipitin titer was not higher than 1:1,000. Scarlet fever antitoxin, given for the twelfth and fourteenth injection, caused no systemic reaction.

In animal 1733 dyspnea, cyanosis and restlessness developed after the second injection of horse serum, and the precipitin titer of its blood serum was up to 1:100, but it remained normal even after subsequent injections of either horse serum or scarlet fever antitoxin.

Animal 1774 never had a positive reaction to the cutaneous test or general reactions and yet died of shock after the fifth injection of horse serum. Its blood serum contained a precipitin titer as high as 1:10,000. Thus, this animal had been sensitized to horse serum.

Animal 1910 had a systemic reaction after the fifth injection of horse serum; its blood serum had a precipitin titer as high as 1:10,000. When scarlet fever antitoxin was injected about fourteen days later, at a time when the reaction to both cutaneous tests was positive, tremors and chills developed. Horse serum injected two weeks later caused no reaction; scarlet fever antitoxin and horse serum injected seven, fourteen and twenty-one days later caused chills only. Five injections were made thereafter, three of normal horse serum and two of scarlet fever antitoxin, but no reactions occurred.

Animal 1776 showed cyanosis and asthmatic breathing after the fifth injection of horse serum, and its blood serum contained a precipitin titer up to 1:1,000. The reaction to the cutaneous test was negative. Scarlet fever antitoxin was given fourteen days later, and only restlessness and hyperpnea were observed. Fourteen days later normal horse serum was again injected, and the animal promptly died in shock.

Only 1 animal, 1776, had a significant response, as shown in table 3. Although the reactions which occurred in this monkey tended to show that antitoxins were innocuous, no definite conclusion could be reached from this one experiment. Only 2 of the animals died as a result of sensitization to horse serum.

COMMENT

Precipitins were found only in animals given injections of horse serum. At no time was the precipitin titer of the blood serum greater than 1:10,000; in most instances it was not even elevated by subsequent injections. Sometimes precipitins appeared in the blood serum after the fourth or the fifth injection, only to disappear after subsequent injections.

Cannon and Marshall [5] stated that the serologic method frequently used for the determination of the precipitin titer of an antiserum, in which serial dilutions of antigen are employed, is "basically illogical" and has been shown to be inaccurate. They listed the types of methods employed by other workers and also described a new method which is serologically more delicate than those hitherto used for the detection of precipitins. It may well be that in some of our specimens we were not able to demonstrate the precipitins present by the tests employed. If the presence of precipitins can be demonstrated even with crude methods, one would expect more positive reactions, even though of a low titer value. Those animals given injections of scarlet fever antitoxin produced no demonstrable precipitin antibodies, unlike every animal given injections of horse serum. Our results with the precipitin test also checked with the negative reactions we obtained to the cutaneous test.

Despite the fact that Macaca mulatta monkeys were given massive injections of scarlet fever antitoxin at intervals of from one or two weeks to a month apart, none died. It appears that the administration of such amounts of antitoxin did not sensitize the animals.

CONCLUSIONS

Macaca mulatta monkeys given massive amounts of purified scarlet fever antitoxin over long periods and at varying intervals did not become sensitized, as shown by the absence of (1) positive reactions to the cutaneous test, (2) decreased precipitin titers in the blood serums and (3) anaphylactoid reactions after subsequent injections.

The purpose of these experiments was to determine whether or not animals sensitized to horse serum would be shocked when given later injections of scarlet fever antitoxin. Such experiments were inconclusive, since too few of the monkeys were sufficiently sensitized to horse serum, although every animal given such injections had some slight increase in the precipitin titer of its blood serum.

5. Cannon, P. R., and Marshall, C. E.: An Improved Serologic Method for the Determination of the Precipitative Titers of Antisera, J. Immunol. **38**:365-376 (May) 1940.

RESPIRATORY METABOLISM IN INFANCY AND IN CHILDHOOD

XXIV. DAILY WATER EXCHANGE OF PREMATURE INFANTS

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Quantitative measurements of the water exchange of premature infants are essential for defining their fluid requirements because of their weak appetites and because factors other than feeding contribute so much to their well-being. This paper presents the results of such measurements made on 12 premature infants fed varying diets but studied under constant environmental conditions.

APPARATUS AND METHODS

A detailed description of the methods employed for analysis of the diet and excreta (urine and feces), for measurement of the twenty-four hour insensible loss from skin and lungs, for determination of the daily respiratory exchange and for calculation of the composition of the metabolic mixture was given in previous papers.[1] The "direct," or "metabolic," method [2] of calculation of the water exchange

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From the New York Hospital and the Department of Pediatrics, Cornell University Medical College.

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An abstract of a part of this paper, with discussion, was published in a previous number of the AMERICAN JOURNAL OF DISEASES OF CHILDREN (**56**:706 [Sept.] 1938).

1. (*a*) Levine, S. Z., and Wheatley, M. A.: Respiratory Metabolism in Infancy and in Childhood: XVII. The Daily Heat Production of Infants; Predictions Based on the Insensible Loss of Weight Compared with Direct Measurements, Am. J. Dis. Child. **51**:1300 (June) 1936. (*b*) Levine, S. Z.; Wheatley, M. A.; McEachern, T. H.; Gordon, H. H., and Marples, E.: Respiratory Metabolism

was used because it gives information concerning not only the total water balance but also the partition of excretion via urine, feces and skin and lungs. According to this method, the total available water of the intake comprises the water ingested as such, the water in solid foods and the water of oxidation. The last equals 0.60 C + 0.41 P + 1.07 F, when C, P and F represent the grams of carbohydrate, protein and fat, respectively, in the metabolic mixture. The total water output comprises the water eliminated through urine, feces and skin and lungs. The water excreted through the skin and lungs is determined by deducting from the total insensible perspiration the difference between exhaled carbon dioxide and inhaled oxygen. $CO_2 - O_2$ is equal to 0.41 C + 0.08 P − 0.08 F. Evidence of the reliability of the method for determining the water exchange of premature infants has already been presented.[1c]

EXPERIMENTAL PROCEDURE

Subjects.—Studies of the water exchange of 9 white and 3 Negro healthy male premature infants while on adequate diets and under practically constant environmental conditions were made in 24 observations of from one to eleven days each for a total of eighty-three days. The ages of the infants ranged from 8 to 60 days and the weights from 1,543 to 2,776 Gm. at the beginning of the observations (table 1).

Diet.—The infants were fed a constant diet of mixtures of human milk or cow's milk for at least two, and usually more, days preceding the onset of observations. The former, with 1 exception (observation 1), consisted of pooled mother's milk, fresh or frozen, boiled for twenty minutes prior to use. The mixtures of cow's milk consisted, with 1 exception (observation 8), of a powdered skimmed milk-olive oil preparation (Olac) diluted with water and for some observations fortified with dextrimaltose. The preparation which was used for infants R. S. and R. Lu. contained one half of the olive oil usually present in Olac.[3] Each infant received 20 drops of concentrate either of vitamin D or of vitamins A and D and 10 to 20 mg. of ascorbic acid daily. The diets permitted average daily weight gains ranging from 20 to 83 Gm. during the different observations.

Environment.—All infants were studied in an air-conditioned room, which permitted practically constant temperature and relative humidity during individual observations. The temperature was maintained between 25 and 25.5 C. (77 and

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in Infancy and Childhood: XXI. Daily Water Exchange of Normal Infants, ibid. **56**:83 (July) 1938. (*c*) Gordon, H. H.; Levine, S. Z.; Marples, E.; McNamara, H., and Benjamin, H. R.: Respiratory Metabolism in Infancy and Childhood: XXII. Water Exchange of Premature Infants; Comparison of Metabolic (Organic) and Electrolyte (Inorganic) Methods of Measurement, J. Clin. Investigation **18**:187 (March) 1939. (*d*) Gordon, H. H.; Levine, S. Z.; Deamer, W. C., and McNamara, H.: Respiratory Metabolism in Infancy and Childhood: XXIII. Daily Energy Requirements of Premature Infants, Am. J. Dis. Child. **59**:1185 (June) 1940.

2. Newburgh, L. H.; Johnston, M. W., and Falcon-Lesses, M.: Measurement of Total Water Exchange, J. Clin. Investigation **8**:161 (Feb.) 1930. Wiley, F. H., and Newburgh, L. H.: Improved Method for the Determination of Water Balance, ibid. **10**:723 (Oct.) 1931.

3. These preparations were supplied by the Mead Johnson Company.

TABLE 1.—*Environmental Conditions, Nutritional Status and Average Daily Diet of Subjects*

Subject	Observation No.	Period of Observation	Environmental Conditions: Average Temperature, C.	Environmental Conditions: Average Humidity, Percentage	Average Rectal Temperature, C.	Initial Age, Days	Nutritional Status: Initial Height, Cm.	Nutritional Status: Initial Weight,* Gm.	Nutritional Status: Average Daily Weight Gain, Gm.	Average Daily Diet: Human Milk,† Gm.	Average Daily Diet: Cow's Milk,‡ Gm.	Average Daily Diet: Dextrimaltose, Gm.	Average Daily Diet: Water, Gm.
		1937											
N. O.	1	3/15-18	25.3	53	36.9	17	44.5	1,912	31	356.5	....	...	.....
E. M.‖	5	4/ 4- 7	25.1	53	37.1	25	46.0	2,083	28	300.2§	....	4.6	.....
	8	4/12-15	25.3	54	37.1	33	....	2,331	33	.....	183.0	8.6	166.0
L. O.‖¶	9	11/ 2- 8	25.0	41	37.1	31	46.0	2,366	47	.....	50.5	16.4	396 6
	12	11/11-13	25.0	40	37.0	40	....	2,776	52	.....	53.9	17.7	433.9
		1938											
H. L.‖	20	1/28-2/4	22.2	40	37.1	23	47.0	2,564	25	.....	72.1	...	291.7
E. C.	25	3/17-20	25.0	45	36.8	13	45.5	2,048	22	353.8	....	...	.....
	26	3/24-26	25.0	40	36.8	20	47.5	2,417	53	.....	64.2	...	309.3
	29	3/30-4/1	25.0	45	37.0	26	....	2,634	47	.....	67.9	...	307.8
R. Le.	30	4/ 7-10	25.5	44	36.8	41	41.5	1,578	20	314.5	....	...	.....
	31	4/13-15	25.2	44	36.8	47	43.0	1,801	61	.....	51.3	...	279.8
	35	4/26-30	25.3	45	36.8	60	46.0	2,372	35	.....	49.0	...	273.0
M. B.	36	5/12-21	25.0	45	36.7	18	42.0	1,716	22	366.1	....	...	.....
	37	5/23-6/3	25.0	45	37.1	29	44.0	1,965	34	478.7	....	...	.....
	38	6/ 6-10	25.0	45	37.1	43	46.0	2,419	42	512.4	....	...	.....
A. P.	39	10/13-17	25.5	45	36.8	17	47.5	2,379	34	.....	52.8	...	278.4
R. E.	42	11/ 8-11	25.5	33	36.9	10	46.0	2,027	42	.....	49.4	...	266.3
G. C.	45	12/ 6- 8	25.5	38	36.4	44	41.0	1,543	28	280.1	....	...	.....
	47	12/10-13	25.5	39	36.3	48	....	1,724	41	.....	46.1	...	227.1
	48	12/14-16	25.5	39	36.3	52	....	1,860	58	.....	46.7	...	228.7
		1939											
R. S.	50	4/13-15	25.0	37	36.3	14	44.5	2,066	43	.....	48.4	...	294.3
	51	4/19-21	25.5	39	36.8	20	45.5	2,247	41	.....	57.4	...	310.3
R. Lu.	53	6/ 4- 6	25.0	62	36.9	8	43.0	1,602	20	277.5	....	...	.....
	56	6/17-18	25.0	42	36.9	21	45.0	2,140	25	.....	53.9	...	298.3

* The recorded weights at birth ranged from 1,130 to 2,220 Gm. Roentgenograms of the lower extremities were obtained for all infants except N. O. and E. M. either just before (E. C., H. L., M. B., R. E., G. C., R. S., R.Lu) or just after study (L. O., R. L., A.P.). The distal epiphysis of the femur was present in all infants except E. C. The proximal epiphysis of the tibia was absent in all except H. L. and R. L. A roentgenogram of the foot was available only for infants H. L., R. L., M. B., R. E., G. C. and R. S. The cuboid bone was absent in all except G. C., in whom it was barely visible. The distal epiphysis of the femur usually appears after the thirty-fifth to the fortieth week of gestation and the proximal epiphysis of the tibia and the cuboid bone at the fortieth week (Growth and Development of the Child: I. General Considerations. White House Conference on Child Health and Protection, New York, Century Company, 1932, sect. 1, p. 67).

† Except in observation 1 the human milk fed was obtained from several sources and pooled. It was boiled for twenty minutes prior to use.

‡ The mixture of cow's milk consisted of a powdered skimmed milk-olive oil preparation (Olac) diluted with water except in observation 8 in which evaporated milk was fed. The mixture used in observations 50, 51 and 56 contained only half the olive oil customarily present in Olac.

§ To this feeding mixture 7.4 Gm. of calcium paracaseinate was added daily.

‖ Negro.

¶ Twin.

78 F.) during all observations except 20. The relative humidity was between 37 and 60 per cent during the different observations.[4]

Clothing.—The clothing worn by the infants during observations consisted of a shirt, gown, specimen belt and stockings, with a diaper wrapped about the head of the smaller infants, and one or two woolen blankets. The amount of clothing worn was kept constant during individual observations, and the average rectal temperatures ranged between 36.3 and 37.1 C. (97.3 and 98.7 F.) (table 1).

RESULTS

Detailed data of the observations are presented in table 2. In table 3 the data in summary are divided into two groups, observations on infants fed human milk and observations on infants fed cow's milk. In each group the observations are arranged in ascending order according to the infants' average weights.

Water Exchange of Thriving Premature Infants Fed Human Milk.—In 9 observations totaling forty days studies were made on 7 infants whose average weights during individual observations ranged from 1,569 to 2,503 Gm. and whose average ages ranged from 9 to 45 days. The human milk fed them supplied an average of 129 calories (range 117 to 153 calories), 2.5 Gm. of protein (range 1.9 to 2.8 Gm.) and 186 Gm. of fluid (range 170 to 224 Gm.) per kilogram of body weight (59 calories, 1.1 Gm. of protein and 2.8 ounces [79.4 Gm.] of fluid per pound [454 Gm.]). These diets permitted satisfactory gains in weight during all observations.

Of the average daily supply of water, totaling 173 Gm. per kilogram (including water of oxidation), 32 Gm. was eliminated through the skin and lungs. The range for the individual observations was from 23 to 47 Gm., but under the environmental conditions of the 9 observations no significant relation was found between age or weight and the amount of water lost through the skin and lungs. Fecal water averaged 10 Gm. and ranged from 5 to 13 Gm., with 2 exceptions (observations 45 and 53), in which loose stools were associated with a loss of fecal water of 20 Gm. per kilogram per twenty-four hours. Urinary water averaged 120 Gm. and ranged from 88 to 158 Gm. per kilogram per twenty-four hours. The significance of these variations will be discussed later. In terms of average percentage distribution of incoming water, 19 per cent was excreted through the skin and lungs, 6 per cent through

4. This range is lower than that maintained in some nurseries for premature infants (60 to 65 per cent) (Blackfan, K. D., and Yaglou, C. P.: The Premature Infant: A Study of the Effects of Atmospheric Conditions on Growth and Development, Am. J. Dis. Child. **46**:1175 [Nov., pt. 2] 1933); it was used to permit observations, as yet incomplete, during which the effect on the water exchange of marked changes in relative humidity, for example, from 40 to 80 per cent, was determined.

TABLE 2.—*Detailed Data on Water Exchange in Terms of Twenty-Four Hours*

Subject	Observation No.	Metabolic Mixture *				Available Water			Outgoing Water				Total Insensible Loss, Gm.	Water Balance, Gm.	Percentage of Gain in Body Weight as Water
		Calories †	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Intake, Gm.	Oxidation, Gm. ‡	Total, Gm.	Total, Gm.	Urine, Gm.	Feces, Gm.	Skin and Lungs, Gm. §			
N. O.	1	109	1	1	24	311	16	326	304	234	25	45	55	22	71
E. M.	5	156	5	4	24	266	21	287	268	188	11	68	78	19	68
	8	162	6	3	26	304	22	325	302	204	29	70	81	23	68
L. O.	9	174	4	0	38	388	25	413	385	277	20	87	103	28	60
	12	200	5	0	43	440	28	468	431	326	8	98	116	37	70
H. L.	20	199	9	0	39	292	27	319	306	161	32	114	130	13	51
E. C.	25	143	1	4	24	310	20	329	314	212	22	80	90	15	67
	26	182	8	1	34	310	25	334	281	133	17	130	145	53	64
	29	197	10	1	36	308	27	335	306	129	17	160	175	29	61
R. Le.	30	113	1	2	22	276	16	292	279	192	10	76	85	13	63
	31	130	4	0	27	280	18	298	255	162	6	86	98	44	72
	35	**156**	**8**	**2**	**26**	**273**	**21**	**294**	271	163	3	104	116	23	68
M. B.	36	123	1	1	26	324	17	341	326	253	14	60	71	15	67
	37	150	1	1	34	422	21	443	422	337	18	67	81	21	60
	38	177	1	3	36	450	25	475	456	365	13	78	92	19	45
A. P.	39	151	6	1	28	279	21	299	281	199	8	74	86	18	54
R. E.	42	148	5	2	26	267	20	287	258	176	10	72	83	29	68
G. C.	45	89	1	0	21	245	13	257	228	147	32	49	58	30	105
	47	112	3	0	24	227	16	243	215	107	10	97	107	28	68
	48	119	5	0	24	229	16	245	210	127	15	68	78	35	61
R. S.	50	130	5	0	27	294	18	312	288	216	4	67	79	25	57
	51	146	6	0	29	310	20	330	312	232	3	78	90	18	44
R. Lu.	53	118	1	4	19	250	16	266	251	179	32	40	47	15	74
	56	162	6	0	33	298	22	321	301	197	5	99	113	20	80

* The metabolic mixture was calculated from the total calories, the urinary nitrogen and the dietary carbohydrate.

† The total calories were determined by combining the results of short observations in the respiration chamber with the daily activity records in all but observations 1, 5 and 8, in which they were estimated from the insensible perspiration.

‡ The water of oxidation was determined from the metabolic mixture by use of the constants of Newburgh [2]: $(P \times 0.41) + (F \times 1.07) + (C \times 0.60)$.

§ The loss of water through skin and lungs was determined by deducting from the toal insensible perspiration the difference between exhaled carbon dioxide and inhaled oxygen [2]: $CO_2 - O_2 = (C \times 0.41) + (P \times 0.08) - (F \times 0.08)$.

TABLE 3.—*Water Balance and Partition of Excretion of Thriving Premature Infants on Adequate Diets of Human Milk or Cow's Milk per Kilogram of Body Weight per Twenty-Four Hours*

Subject	Observation No.	Duration of Observation, Days	Average Age, Days	Average Weight, Gm.	Average Surface Area, Square Meters *	Daily Diet			Metabolic Mixture, Total Calories	Available Water, Gm.‡	Partition of Outgoing Water							
						Protein, Gm.	Calories	Fluid, Gm.†			Urine		Feces		Skin and Lungs		Water Balance	
											Gm.	% §	Gm.	% §	Gm.	% §	Gm.	% §
Infants Fed Human Milk																		
G. C.	45	2	45	1,569	0.129	2.8	117	179	57	164	94	57	20	12	31	19	19	12
R. Le.	30	3	42	1,608	0.132	2.1	141	196	70	182	119	65	6	3	47	26	8	4
R. Lu.	53	2	9	1,622	0.133	2.0	119	171	73	164	110	67	20	12	25	15	9	6
M. B.	36	9	22	1,797	0.143	2.1	122	204	68	190	141	74	8	4	33	17	8	4
N. O.	1	3	19	1,959	0.153	2 7	123	182	56	166	119	72	13	8	23	12	11	7
E. C.	25	3	14	2,081	0.160	1.9	126	170	69	158	102	65	11	7	38	24	7	4
E. M.	5	3	26	2,126	0.162	4.5‖	102	146	73	135	88	65	5	4	32	24	9	7
M. B.	37	11	34	2,137	0.163	2.4	153	224	70	207	158	76	8	4	31	15	10	5
M. B.	38	4	45	2,503	0.184	2.1	145	205	71	190	146	77	5	3	31	16	8	4
Average			28	1,934	0.151	2.5	129	186	67	173	120	69	10	6	32	19	10	6
Infants Fed Cow's Milk																		
G. C.	47	3	49	1,788	0.143	6.0	125	153	63	136	60	44	6	4	54	40	16	12
R. Le.	31	2	48	1,802	0.147	6.4	134	178	70	160	87	54	3	2	46	29	24	15
G. C.	48	2	53	1,918	0.150	5.6	118	144	62	128	66	52	8	6	35	27	18	14
R. E.	42	3	11	2,089	0.160	5.5	115	151	71	137	84	61	5	4	34	25	14	10
R. S.	50	2	15	2,109	0.162	4.8	100	162	62	148	102	69	2	1	32	22	12	8
R. Lu.	56	1	21	2,152	0.164	5.2	109	163	75	149	92	62	2	1	46	31	9	6
R. S.	51	2	20	2,287	0.172	5.2	110	160	64	144	101	70	1	0	34	24	8	6
E. M.	8	3	34	2,381	0.177	4.8	120	150	68	136	86	63	12	9	29	21	10	7
R. Le.	35	4	62	2,441	0.180	4.7	98	132	64	120	67	56	1	1	43	36	9	8
A. P.	39	4	19	2,447	0.181	5.0	105	135	62	122	81	66	3	2	30	25	7	6
L. O.	9	4	33	2,494	0.183	4.4	124	182	70	166	111	67	8	5	35	21	11	7
E. C.	26	2	21	2,501	0.184	6.0	125	149	73	134	53	40	7	5	52	39	21	16
H. L.	20	7	27	2,651	0.192	5.9	121	137	75	120	61	51	12	10	43	36	5	4
E. C.	29	2	27	2,680	0.193	5.9	123	141	74	125	48	38	6	5	60	48	11	9
L. O.	12	2	41	2,829	0.201	4.1	118	181	71	165	115	70	3	2	35	21	13	8
Average			32	2,309	0.173	5.3	116	155	68	139	81	58	5	4	41	30	13	9

* The surface area was calculated from the formula given by A. D. Klein and R. E. Scammon: Relations Between Surface Area, Weight and Length of the Human Body in Prenatal Life, (Proc. Soc. Exper. Biol. & Med. **27**: 456, 1930): $5.188\ W + {}^{0.75}$.

† Total weight of intake.

‡ Includes ingested water and water of oxidation.

§ The figures in these columns represent percentages of available water.

‖ Calcium paracaseinate was added.

the feces and 69 per cent through the urine. The water retained in the body averaged 10 Gm. (range 7 to 19 Gm.) per kilogram per twenty-four hours, or 6 per cent of the incoming water (table 3). In percentages of gain in body weight (table 2), the water retained averaged 69 per cent and ranged from 45 to 74 per cent, with 1 exception (observation 45).

Water Exchange of Thriving Premature Infants Fed Cow's Milk.—In 15 observations totaling forty-three days studies were made on 10 infants whose average weights during individual observations ranged from 1,788 to 2,829 Gm. and whose average ages ranged from 11 to 53 days. The diets contained 116 calories (range 98 to 134 calories),

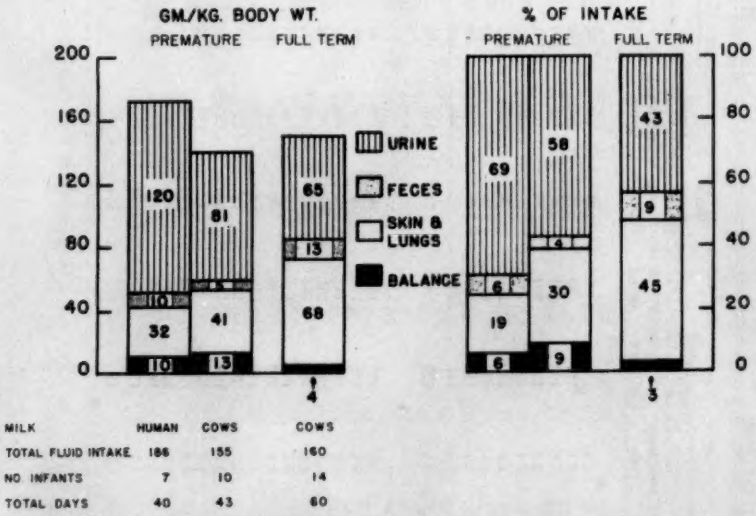

Chart 1.—Water balance of premature and full term[1b] infants on adequate diets. The total height of the columns indicates the total amount of incoming water; the vertically lined compartments, the output of water in the urine; the dotted areas, fecal water, and the blank areas, loss of water through the skin and the lungs. The difference between incoming and outgoing water is designated by the shaded areas and represents accretions in the body water. The premature infants fed human milk averaged 1.9 Kg. in weight and received 129 calories and 2.5 Gm. of protein per kilogram per twenty-four hours. The premature infants fed cow's milk averaged 2.3 Kg. in weight and received 116 calories and 5.3 Gm. of protein per kilogram. The full term infants fed cow's milk weighed 6.8 Kg. and received 118 calories and 4.8 Gm. of protein per kilogram. The total calories catabolized by the three groups of infants averaged 67, 68 and 82, respectively, per kilogram per twenty-four hours.

5.3 Gm. of protein (range 4.1 to 6.4 Gm.) and 155 Gm. of total fluid (range 132 to 182 Gm.) per kilogram of body weight per twenty-four hours (53 calories, 2.4 Gm. of protein and 2.3 ounces [65.2 Gm.] of fluid per pound).

Of the average total of 139 Gm. of available water per kilogram, 41 Gm. (range 29 to 60 Gm.) was eliminated through the skin and lungs. Fecal water averaged 5 Gm. and ranged from 1 to 12 Gm. per kilogram. Urinary water averaged 81 Gm. and ranged from 60 to 115 Gm. per kilogram per twenty-four hours. In terms of percentages of incoming water, 30 per cent was eliminated through the skin and lungs, 4 per cent through the feces and 58 per cent through the urine. The water retained in the body averaged 13 Gm. (range 5 to 24 Gm.) per kilogram per twenty-four hours and represented 8 per cent of the intake of water. In percentages of gain in body weight (table 2), retained water averaged 63 per cent and ranged from 54 to 80 per cent, with 1 exception (observation 51).

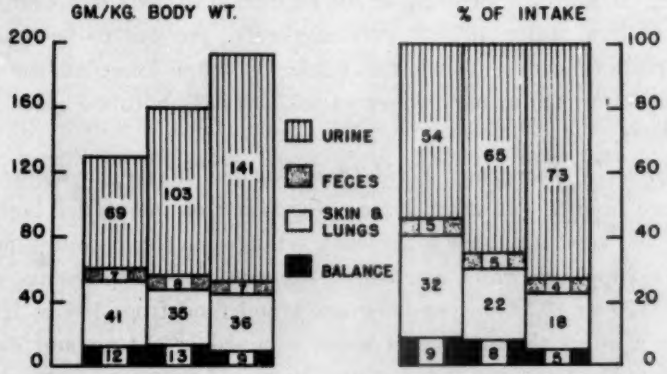

Chart 2.—Effect of increasing fluid intake on water exchange of premature infants. The infants with the lowest fluid intake (range 132 to 153 Gm. per kilogram) weighed 2.3 Kg. and received 115 calories and 5.4 Gm. of protein per kilogram. The infants with the intermediate fluid intake (range 160 to 182 Gm. per kilogram) weighed 2.1 Kg. and received 118 calories and 3.9 Gm. of protein per kilogram. The group of infants with the highest fluid intake (range 196 to 224 Gm. per kilogram) received 143 calories and 2.2 Gm. of protein per kilogram. The total calories catabolized were virtually the same for each group, 69, 67 and 70, respectively.

Comparison with Results of Studies on Full Term Infants.—In chart 1 the results of the studies on the water exchange of premature infants fed human milk and of those fed cow's milk are compared graphically with the results previously reported from this laboratory for full term infants fed cow's milk.[1b] All three groups of infants were thriving under average dietary and environmental conditions and were wearing an average amount of clothing and had positive water balances

of 10, 13 and 4 Gm. per kilogram, which comprises 69, 63 and 70 per cent, respectively, of the gains in weight. There are, however, significant differences in the partition of excretion, for the two groups of premature infants excreted only 32 and 41 Gm., respectively, of water per kilogram through the skin and lungs as against 68 Gm. per kilogram for the full term infants. The differences of 36 and 27 Gm. are fourteen and eleven times as great as the probable error of the respective differences. The lower total loss of water through the skin and lungs in premature infants is probably related to their lower total production of heat per kilogram of body weight (67 and 68 as compared with 82 calories per kilogram), their relatively larger radiating surface and their smaller amount of insulating, fatty tissue, factors which would tend to lessen the need for sweating in the regulation of body temperature. The loss of fecal water did not vary markedly. As was to be expected in observations during which the intake of water exceeded the minimal requirement, the urinary water varied inversely with the insensible loss of water.

Effect of Increasing Fluid Intake on the Water Exchange of Premature Infants.—In chart 2 the observations on infants fed both human milk and cow's milk are graphically arranged in three groups, according to the supply of water available. Augmentation of the intake of water from 129 to 192 Gm. per kilogram (total fluid from 144 to 207 Gm.) did not affect the amount of water retained or the amount eliminated through the feces and the skin and lungs. The urinary water, however, rose progressively from 69 to 141 Gm. per kilogram per twenty-four hours. These results are similar to those found in investigations on full term infants.[1b]

COMMENT

These quantitative studies of water exchange afford more accurate information than was heretofore available concerning the fluid requirements of premature infants. To meet the needs of a growing organism, sufficient water must be supplied to insure renal regulation of osmotic pressure and acid-base balance in the body and excretion of metabolic waste products, to permit the loss of water through skin and lungs, both by seepage and by active secretion of sweat glands, to cover fecal excretion and, finally, to leave a surplus for retention in the construction of new body tissue. These observations indicate that under ordinary dietary and environmental conditions and with the wearing of an ordinary amount of clothing the administration of a total of approximately 165 Gm. of fluid per kilogram (2.5 ounces [70.9 Gm.] per pound) covered all these requirements and permitted the retention of water in

amounts which constituted approximately 65 per cent of the total gain in body weight, a figure corresponding to that found in infantile tissues by chemical analyses.

Before accepting this average figure of 165 Gm. per kilogram as an arbitrary standard of the amount of fluid needed for the feeding of premature infants, one may well inquire whether administration of greater or lesser amounts carries any particular advantages or disadvantages. In chart 2 it is seen that administration of larger amounts of fluid was followed by increased excretion in the urine and had no effect on the retention of fluid in the body, on the loss of fecal water or on the loss through skin and lungs. In observations 20, 35 and 39, for example, in which 132 to 141 Gm. of fluid per kilogram (2 ounces [56.7 Gm.] per pound) was administered, adequate fluid was available to permit as satisfactory retention of water as occurred in observations 36, 37 and 38, in which 204 to 224 Gm. per kilogram (3 ounces [85 Gm.] per pound) was fed (table 3). Since many premature infants, particularly those who are young or small, have defective sucking ability and tire easily and since the ingestion of excessive fluid may lead to regurgitation and aspiration or to overdistention of the stomach, with consequent respiratory embarrassment, it appears desirable to feed the minimum amount of fluid which will cover the needs of the body under usual conditions of environment and organic and inorganic intake of food and leave an adequate margin of safety for times of stress.

Since the kidney is the organ charged with the responsibility of maintaining proper osmotic relations [5] in the body and excreting waste products [6] in the face of such stresses as diarrhea, vomiting, low intakes of fluid and excessive perspiration, it is worth pointing out that at any given level of fluid intake above the minimum, the lower loss of water through skin and lungs by premature infants makes available approximately 30 Gm. of water per kilogram more for urinary flow. Whether this can be interpreted as indicating that a lower fluid intake is permissible for premature infants than for full term infants awaits further studies of the effect of water deprivation on renal function. One is justified in concluding, however, that until the premature infant's increasing vigor permits use of his appetite as a guide to fluid requirements, one need not administer more than is customarily given to a full term infant.

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5. Gamble, J. L.: Extracellular Fluid: Extracellular Fluid and Its Vicissitudes, Bull. Johns Hopkins Hosp. **61**:151 (Sept.) 1937; Extracellular Fluid: Renal Defense of Extracellular Fluid; Control of Acid-Base Excretion and the Factors of Water Expenditure, ibid. **61**:174 (Sept.) 1937.

6. Schloss, O. M.: Intestinal Intoxication in Infants: The Importance of Impaired Renal Function, Am. J. Dis. Child. **15**:165 (March) 1918.

SUMMARY

Metabolic measurements of the water exchange were made in 24 observations of from one to eleven days each for a total of eighty-three days on 12 thriving premature infants whose average ages ranged from 9 to 62 days and whose average weights ranged from 1,569 to 2,829 Gm. during the individual observations.

With average diets of human milk which supplied 129 calories, 2.5 Gm. of protein and 186 Gm. of fluid per kilogram and ordinary environmental conditions and with the wearing of ordinary amounts of clothing, 120, 10 and 32 Gm. of water per kilogram of body weight were eliminated through the urine, the feces and the skin and lungs, respectively. In terms of percentages of total incoming water (173 Gm.), 69 per cent was excreted through the urine, 6 per cent through the feces and 19 per cent through the skin and lungs.

With diets of cow's milk which supplied 116 calories, 5.3 Gm. of protein and 155 Gm. of fluid per kilogram, 81, 5 and 41 Gm. of water per kilogram of body weight were eliminated through the urine, the feces and the skin and lungs, respectively. These quotas represented 58, 4 and 30 per cent of the total water intake (139 Gm.).

In each group of observations, adequate water was available to permit retention of 10 and 13 Gm. per kilogram of body weight, representing 69 and 63 per cent of the gain in body weight.

Comparison of the results of these studies with those from studies made on thriving older, full term infants under average conditions of diet and environment showed that premature infants fed human milk and those fed cow's milk excreted 36 and 27 Gm. less water per kilogram by way of the skin and lungs, leaving more water for urinary flow.

Augmentation of the fluid intake from 144 to 207 Gm. per kilogram increased the urinary output but did not affect the retention in the body or the loss of water through the feces and the skin and lungs.

CONCLUSIONS

Under ordinary conditions of environment and organic and inorganic intake of food, and with the wearing of ordinary amounts of clothing, the administration to healthy premature infants over 1 week of age of approximately 165 Gm. of fluid per kilogram (2.5 ounces per pound) supplies adequate water for excretion through the kidneys, intestines and the skin and lungs and for the construction of body tissues.

525 East Sixty-Eighth Street.

Case Reports

TYPE V PNEUMOCOCCIC MENINGITIS COMPLICATED BY LEFT CAVERNOUS SINUS THROMBOSIS

REPORT OF A CASE IN WHICH RECOVERY FOLLOWED COMBINED TREATMENT WITH SPECIFIC SERUM AND SULFAPYRIDINE SODIUM

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AND
JOHN F. ROBINSON, M.D.
GREENVILLE, S. C.

Since the introduction and use of sulfapyridine in the treatment of pneumococcic infections, increasingly numerous reports have appeared in the literature of the excellent results obtained, especially in cases of pneumococcic meningitis, a disease heretofore considered almost 100 per cent fatal.

A recent review of the literature,[1] however, failed to disclose any case of recovery from meningitis caused by the type V pneumococcus and complicated by thrombosis of the left cavernous sinus.

In reporting this case we wish to call attention to the combined treatment with specific serum and sulfapyridine sodium,[2] a soluble monohydrate sodium salt of sulfapyridine for intravenous use, which proved valuable as the patient was unable to retain sulfapyridine when administered by mouth. Transfusions of citrated blood were given to combat anemia and to prevent the toxic effects of the drug, of which 785 cc. of a 5 per cent solution (39.25 Gm.) was given over a period of thirty-seven days.

We are able to report a case of this infection, until recently universally fatal, in which recovery followed nine weeks of intensive combined treatment.

From the Department of Pediatrics, St. Francis Hospital.

1. Hodes, H. L.; Gimbel, H. S., and Burnett, G. W.: Treatment of Pneumococcic Meningitis with Sulfapyridine and Sodium Salt of Sulfapyridine, J. A. M. A. **113**:1614-1619 (Oct. 28) 1939. Hewell, B. A., and Mitchell, A. G.: Treatment of Pneumococcus Meningitis with Sulfanilamide, J. A. M. A. **112**:1033-1037 (March 18) 1939. Stein, J. L., and Steiner, M. M.: Meningitis Caused by Pneumococcus Type III, Am. J. Dis. Child. **58**:274-281 (Aug.) 1939. Welch, S. H., and Martin, H. F.: Pneumococcus Type III Meningitis with Recovery, J. Pediat. **15**:563-571 (Oct.) 1939.

2. The sulfapyridine sodium was furnished by the Abbott Laboratories, North Chicago, Ill.

REPORT OF CASE

Jean T., a 6 year old white girl, was admitted to the St. Francis Hospital the afternoon of Feb. 29, 1940. with the following history. Two weeks before she had had an acute influenzal infection with earache, which apparently cleared up without incision or drainage. Suddenly, three days before admission she became ill, with severe headache, nausea and vomiting. She grew progressively worse. On admission she was acutely ill and semistuporous and lay with head retracted and knees drawn up. She resented any movement and would rouse enough to complain of pain in the head and neck. On direct questioning she would answer.

Physical Examination.—Head and Eyes: The head was retracted; there were rigidity and resistance to flexion of the neck, associated with pain. The right eye was normal in appearance and exhibited normal movements. The pupil was dilated and reacted slowly to light. The left eye showed purple discoloration of the lids, with edema, marked ophthalmia and downward deviation of the ball; the pupil was not seen. Tension was apparently roughly equal in the two eyes. The patient complained of severe pain on pressure and on exposure of the left eye to bright light.

Ears: Both were normal, with the drums in good position and only slightly pink. There was no perforation or drainage from either ear.

Mouth: The tongue was heavily coated; the teeth were in good condition; the tonsils and pharynx were moderately injected.

Chest: The chest was normal in shape, with no beading. Respiration was regular. Expansion was equal on the two sides, and the pulmonary fields were clear on percussion and auscultation.

Heart: The rate was rapid, with a regular rhythm. No murmurs or enlargement was present.

Abdomen: The abdomen was soft with no masses or tenderness. The liver and spleen were not palpable.

Genitalia: The genitalia were normal to inspection.

Extremities: There was no deformity, edema or involvement of the joints.

Neurologic Examination.—Kernig and Brudzinski signs were elicited; the knee jerks were active; there was slightly sustained ankle clonus; tache cérébrale was present.

Laboratory Data.—On admission, examination of the blood gave the following data: the hemoglobin content was 77 per cent (12.6 Gm., Dare); the red cells numbered 3,530,000 and the leukocytes 18,600 per cubic millimeter, with 97 per cent polymorphonuclears and 3 per cent lymphocytes. The color index was 1.1. Culture of the blood taken after three days was sterile.

Examination of the spinal fluid showed 583 cells per cubic millimeter, with 95 per cent polymorphonuclear leukocytes and 5 per cent lymphocytes. The reaction for sugar was negative, and that for globulin was 4 plus. Both the smear and the culture of the spinal fluid showed pneumococci.

On the basis of these data a diagnosis of pneumococcic meningitis complicated by thrombosis of the left cavernous sinus or empyema of the ethmoid or sphenoid sinuses was made. Consultants from the medical and ophthalmo-otolaryngologic departments concurred in the diagnosis.

The child was sensitive to horse serum, and the specific rabbit serum was not immediately available. We therefore decided to give sulfapyridine sodium intravenously in the dose suggested by the manufacturer. Several times during the child's stay in the hospital oral administration of sulfapyridine was attempted, but she could never retain the drug. Therefore, it was necessary to continue to give the drug intravenously throughout the entire course of treatment. Within twelve

TABLE 1.—*Laboratory Data*

	Spinal Fluid						Blood						
Date	Cells per Cubic Mm.	Polymorphonuclear Leukocytes, Percentage	Lymphocytes, Percentage	Globulin	Sugar	Smear and Culture	Hemoglobin Content, Percentage	Red Blood Cells per Cubic Mm.	White Blood Cells per Cubic Mm.	Polymorphonuclear Leukocytes, Percentage	Lymphocytes, Percentage	Culture, After 48 Hours	Color Index
2/29.....	583	95	5	++++	0	+	77	3,530,000	18,000	92	3	—	1.1
3/ 1.....	1,269	85	15	++++	0	+	..	.....	.....	..	..	..	..
3/ 2.....	...	..	..	.....	..	..	75	.....	13,650	80	20	..	..
3/ 3.....	541	67	33	++++	Trace	+	..	.....	.....	..	..	..	..
3/ 5.....	1,142	89	11	++++	Trace	—	48	.....	15,900	71	29	..	..
3/ 8.....	365	86	14	.....	..	..	..	.....	.....	..	..	..	..
3/11.....	1,388	89	11	+++	+	+	65	3,930,000	21,000	86	14	—	.83
3/13.....	4,329	89	11	++++	+	+	65	.....	18,350	80	20	..	...
3/16.....	353	75	25	++++	+	+	..	3,320,000	.....	..	..	..	1.0
3/17.....	...	..	..	.....	..	..	55	.....	10,800	73	27	..	...
3/19.....	860	59	41	++++	0	—	68	3,550,000	14,150	76	24	..	...
3/21.....	521	58	42	+	Trace	—	..	2,620,000	.....	..	..	..	...
3/24.....	541	80	20	+	Trace	—	..	3,650,000	.....	..	..	..	...
3/25.....	...	..	..	.....	..	..	65	.....	11,500	75	25	..	...
3/26.....	277	90	10	++	Trace	—	..	3,640,000	.....	..	..	..	1.0
3/28.....	329	86	14	+	Trace	—	..	.....	.....	..	..	..	..
3/30.....	58	80	20	+	Trace	—	67	.....	7,900	79	21	..	...
4/ 3.....	8	86	14	+	Trace	—	..	.....	.....	..	..	..	..
4/ 5.....	...	..	..	.....	..	..	70	.....	7,700	70	30	..	...
4/ 9.....	...	..	..	.....	..	..	72	.....	8,000	48	52	..	...
4/24.....	...	..	..	.....	..	..	80	.....	7,600	52	48	..	...

hours there was a definite and gratifying improvement in her condition; the temperature dropped from 105 F. to 100 F., the sensorium became clearer and there was no increase in the ocular disturbance.

In the accompanying tables data are given relating to the examinations of the spinal fluid and the blood and the therapy used during the patient's six week stay in the hospital—intravenous administration of sulfapyridine sodium and specific serum and blood transfusion. Owing to lack of laboratory facilities, concentrations of sulfapyridine in the blood and spinal fluid were not determined. The only toxic effects noted were transient hematuria on two occasions and moderately severe anemia, with a red cell count of 2,620,000 on March 30.

TABLE 2.—*Therapy*

	Sulfapyridine Sodium, 5 per Cent Solution Given Intravenously									
Date.....	2/29	3/1	3/2	3/5	3/11	3/13 a. m.	3/14	3/15	3/16	3/17
Amount, cc..	25	25	25	25	25	20 p. m. 20	20	20	20	20
Date.....	3/19	3/20	3/21	3/22	3/23	3/24	3/25	3/26	3/27	
Amount, cc..	a. m. 20 p. m. 20	a. m. 20 p. m. 20	a. m. 20 p. m. 20	a. m. 20 p. m. 20	a. m. 20 p. m. 20	a. m. 20 p. m. 20	a. m. 20 p. m. 20	25	25	
Date.....	3/28	3/29	3/30	3/31	4/1	4/2	4/3	4/5	4/7	
Amount, cc..	25	25	25	25	25	25	20	20	20	
	Type V Antipneumococcus Serum * (Rabbit)									
Date.....	3/3	3/4	3/5	3/6	3/9	3/11	3/12	3/13		
Amount, units....	20,000	20,000	20,000	20,000	20,000	20,000	20,000	20,000		
Date.....	3/16	3/23	3/24	3/25	3/26	3/27	3/28	3/29		
Amount, units....	20,000	20,000	20,000	20,000	20,000	20,000	20,000	20,000		
	Transfusion of Citrated Whole Blood									
Date.....	3/7	3/14	3/20	3/26	4/1					
Amount, cc.....	300	300	300	300	340					

* Total amount given was 320,000 units.

SUMMARY

A case of pneumococcic meningitis complicated by thrombosis of the left cavernous sinus is reported. So far as we can learn, ours is the first patient with this condition to recover.

Treatment consisted of the combined use of specific serum and large amounts of sulfapyridine sodium, given intravenously, with transfusion of whole blood.

Five months has elapsed since recovery, and to date (Aug. 2, 1940) the patient remains well.

The case is reported with the hope that the plan of therapy followed successfully may prove of value in similar cases in the future.

Dr. Everett Poole, of the medical department, and Dr. J. W. Jervey Jr., of the ophthalmo-otolaryngologic department, assisted in the management in this case. Dr. T. R. W. Wilson, pathologist of the Greenville General Hospital, typed the pneumococcus.

307 East Coffee Street.

TUBERCULOSIS OF THE URACHUS WITH EXTENSIVE INTESTINAL AND PERITONEAL TUBERCULOSIS

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MEMPHIS, TENN.

Persisting portions of the urachus are among the more significant anomalous remnants of the embryonic urinary tract. In the medical literature only 3 reports of tuberculosis of the urachus could be found; in each, the disorder occurred in a woman who subsequently gave no evidence of progressive tuberculosis of other organs. This is the fourth case to be described and is the only instance in which a tuberculous urachus is reported to occur in a boy and in association with unusual manifestations of tuberculosis in other sites.

REVIEW OF THE LITERATURE

In 1899, Briddon and Eliot [1] excised an infected urachus in a 19 year old married woman, and on histologic examination made the diagnosis of tuberculosis. There was no history of previous contact with tuberculosis. Five weeks before admission, pain, redness and heat had occurred over what formerly was a normal navel. A small, pea-sized swelling formed at the umbilicus during the next two weeks, accompanied by constant severe, lancinating hypogastric pains, marked vesical tenesmus, slight hematuria and urinary frequency (every hour). The swelling opened spontaneously and discharged urinous fluid, followed by relief of pain and subsidence of the swelling. Four days later, practically all urine passed through the umbilical opening. There were marked loss of weight and weakness. Examination in the hospital showed nothing abnormal except tenderness over the region of the bladder and the presence of the umbilical fistula. The urine was alkaline, had a foul ammoniacal odor and contained albumin, blood, mucus, pus, bladder cells and triple phosphate crystals. A sound could be passed freely through the fistula from the umbilicus to the bladder. Suprapubic cystotomy was performed for

From the Laboratories and the Department of Pediatrics of the Mount Sinai Hospital, New York.

1. Briddon, C. K., and Eliot, E.: Tubercular Degeneration of the Patent Urachus in the Adult, M. & S. Rep. Presbyterian Hosp. 4:30-38, 1900.

relief of the cystitis, and the urachus could be seen opening into the anterior portion of the dome of the bladder. Ulcers on the posterior wall of the bladder showed "no evidence of tuberculosis." After a period of suprapubic drainage, the urachus was extirpated without opening the peritoneum. The wall of the urachus was ¼ inch (0.6 cm.) in thickness. The wound closed slowly but eventually healed completely, with much improvement in the patient's general condition. Since no evidence of other tuberculous foci was found, the authors expressed the belief that the tuberculosis was primary in the urachus, with secondary involvement of the bladder, which produced the severe cystitis.

Pearce and Miller [2] reported a second case, in 1912. A 26 year old unmarried woman with a history of hacking cough for several years had noted a discharging sinus, ½ inch (1.3 cm.) below the umbilicus, four years previously. It had closed spontaneously. Four weeks before examination a small, red, tender, inflammatory tumor occurred at the inner margin of the umbilicus. Severe coryza and cough developed, lasting three days, during which time the abdominal mass enlarged rapidly to 2 inches (5 cm.) in width and 3 inches (7.6 cm.) in length. The mass ruptured, and a mucopurulent discharge escaped through the midline opening, with relief of tenderness. At examination, the patient appeared well nourished; the temperature was 101.2 F., the hemoglobin concentration 75 per cent and the white cell count 5,000 per cubic millimeter; results of urinalysis were normal. Apical dulness of the right lung, with many fine moist rales accentuated by coughing, was present but did not change during the stay in the hospital. Examination of the sputum was constantly negative for tubercle bacilli. A diamond-shaped, indurated tumor, 2 inches (5 cm.) in width, extended 2½ inches (6.4 cm.) below the umbilicus in the midline of the abdominal wall. On pressure there was a mucopurulent discharge from the center of the umbilicus. The edge of the opening was red and elevated, with excoriation of ½ inch (1.3 cm.) of the surrounding skin. A probe met resistance below the central part of the tumor. The mass was excised and contained an accumulation of hard sebaceous material, the size of a "hen's egg." Twenty-four hours later severe, generalized pruritus and scarlatiniform, erythematous efflorescence occurred, which subsided in four days, after an elevation of temperature from 100 to 104.8 F. There was sudden gross hematuria on the sixth postoperative day, both on voiding and on catheterization, although clear urine was passed three hours before this incident. Cystoscopy showed clear urine spurting from both ureteral orifices, but blood exuded from an aperture in the

2. Pearce, H. E., and Miller, E. L.: Hematuria from Tuberculosis of a Patent Urachus: Operation Followed by Septic Rash; Recovery, J. A. M. A. **58**: 1684-1685 (June 1) 1912.

fundus, the margins of which appeared indurated and excoriated, suggesting tuberculosis. Eight days after the first operation, the remainder of the infected urachus and the wall of the bladder for 1 inch (2.54 cm.) around the orifice were excised. Twenty-four hours later a pruritic eruption developed, similar to that occurring after the first operation; this also subsided in four days. The operative wound healed perfectly. Histologic diagnosis was tuberculosis of the urachus. No explanation for the postoperative episodes of pruritus and eruption could be given. The authors reported this case as illustrating a rare cause of hematuria and as an unusual instance of tumefaction of the abdominal wall.

The third case of tuberculosis of the urachus was noted by Eastman,[3] in 1915, in a 19 year old married woman. The past history included one uneventful pregnancy and no suggestion of tuberculosis. There were no urinary difficulties. Ten months before admission, while working in the garden, the patient felt midline infraumbilical pain. A lump, the size of a small apple, developed but did not enlarge. Slight tenderness persisted for three months, without much actual pain or soreness. An opening of pinpoint size appeared in the midline of the abdomen, halfway between the umbilicus and the pubis. Clear, watery, odorless fluid discharged for one week periods, which alternated with intervals without discharge, during which a crust covered the opening. The size of the tumor did not change, and tenderness persisted. Examination showed no sign of tuberculosis, and the results of urinalysis were normal. A small sound, passed downward through the discharging sinus, met impassable resistance behind the symphysis pubis. At operation, the preperitoneal fistulous tract was dissected out; it crossed the space of Retzius, to end as a thin cord attached to the anterior wall of the bladder in the midline near the vesicourethral junction. The excised specimen was a thin-walled, tubular structure, with an ulcerated mass, 2 cm. in width, on the dorsal wall of the tract near its cutaneous orifice. Histologically, this area showed well developed tuberculous granulation tissue. The wound healed slowly, but there was no recurrence. Cystoscopic examination showed a normal bladder. The urine was normal.

REPORT OF A CASE

A 3 year old white boy was first admitted to the pediatric service of Dr. Béla Schick Oct. 8, 1938 because of "spiking" fever, abdominal distention and moderate diarrhea. The past history included an instrumental delivery and impetigo shortly after birth. He had been vaccinated against smallpox and had been immunized against diphtheria and pertussis. No family history of tuberculosis was obtained. He had had occasional attacks of urticaria during the summer months.

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3. Eastman, J. R.: Tuberculosis of the Urachus, Am. J. Obst. **72**:640-645, 1915.

Six weeks before admission, diarrhea developed consisting of four to six loose movements a day for three days. There was no associated abdominal pain, fever, nausea or vomiting. The stools contained no blood. Others in the family had no diarrhea at this time. A two week period of complete subsidence of the diarrhea was followed by a recurrence, which lasted two weeks. The latter episode ended two weeks before admission but was followed by a daily elevation of temperature to from 100 to 103 F. Urinary frequency occurred one week before admission and responded to mandelic acid therapy. The elevated temperature persisted.

On examination, the child appeared pale. There was no lymphadenopathy. The heart and lungs were normal. The abdomen had a doughy consistency on palpation and was held in moderate voluntary rigidity. There was a sensation of resistance to palpation of the suprapubic region. Results of rectal examination were normal. No masses or viscera were palpable.

Laboratory studies showed a hemoglobin concentration of 62 per cent, a red cell count of 5,200,000 and a white cell count of 16,700 per cubic millimeter, with a normal differential count. Results of urinalysis were normal. The reaction to the Mantoux test was markedly positive. The reaction to the patch test for tuberculosis was also positive. Results of a cutaneous test for Brucella and agglutination tests for the typhoid-dysentery group of organisms were negative. A roentgenogram of the chest showed only slight exaggeration of the pulmonary markings at the bases of both lungs. No abnormalities were visible on a simple roentgenogram of the abdomen. A barium sulfate enema showed no obstruction or constriction of the colon. Markedly irregular filling defects of the cecum were thought to be due to fecal material. The terminal portion of the ileum was visualized for a distance of 2 inches (5 cm.) and appeared adherent to the caput coli. The barium meal showed a normal appearance of the stomach and duodenum. Special study of the small intestine revealed no abnormalities; the terminal portion of the ileum showed no pathologic changes.

Enterococcus was cultured from the stools. Repeated examinations of the stools showed a positive reaction to the guaiac test only once. Results of the inoculation of a guinea pig with material from a gastric lavage were negative for tubercle bacilli.

The patient's temperature ranged from 99 to 100 F. during his seventeen day stay in the hospital; he was discharged October 25. A tuberculous intra-abdominal process was considered the most likely diagnosis because of the positive reaction to the tuberculin test at this age, the recurrent diarrhea and the fever.

Second Admission.—Two weeks later, on November 10, the child was readmitted because of persistent fever (temperature from 100 to 103 F.), three to four yellowish stools daily and marked anorexia. At this time, examination revealed a child who appeared chronically ill, with moderately sunken eyes. The abdomen was distended and of doughy consistency. Rectal palpation showed a firm mass, high on the right side. The reaction to a tuberculin patch test was again markedly positive. The hemoglobin concentration was 70 per cent, the red cell count 4,300,000 and the white cell count 19,100 per cubic millimeter, with 68 per cent polymorphonuclear leukocytes. Results of urinalysis were normal; culture of the urine showed Staphylococcus albus B. Results of the inoculation of a guinea pig with urine and examination of a concentrated specimen of urine for acid-fast bacilli were negative.

Transfusion of 250 cc. of blood was followed by remission of the fever for one week. In the third week after admission, the temperature rose to 102 F., and there were dulness, diminished breathing and a few medium, moist rales at the base of

the right lung. A roentgenogram of the chest showed pneumonic infiltration in the right lung extending from the hilus toward the lower lobe. These physical signs gradually disappeared. There was no further diarrhea; nourishment was taken fairly well, and the weight remained essentially stationary. Although a low grade fever persisted, it was believed that nothing further in a diagnostic or therapeutic way could be accomplished in the hospital, and therefore the patient was discharged on December 14.

Third Admission.—On Feb. 16, 1939, the child was admitted for the third time. He had been taken to Florida after his previous discharge and had been fairly well except for almost daily crampy umbilical pains of ten to fifteen minutes' duration. There were slight urinary frequency and dysuria two weeks before admission, which subsided in a few days, but two days after their onset a red,

Fig. 1.—Bulging subumbilical mass, before incision and drainage.

tender swelling was noticed in the umbilical area, which became intermittently larger and smaller. Some diminution in appetite occurred during this episode.

Examination showed that he was poorly nourished and appeared chronically ill. Small cervical and inguinal lymph nodes were palpable. The abdomen was soft. A moderately firm, slightly tender, circumscribed globular mass, about 4 cm. in diameter, was fixed to the skin of the anterior abdominal wall and pushed the umbilicus upward (fig. 1). Cloudy fluid was aspirated from this mass, and on culture Streptococcus viridans was found. No acid-fast organisms were seen on smear; inoculation of a guinea pig was uninformative because the animal died too soon.

The urine was loaded with white blood cells and had an acid reaction. Culture showed Str. viridans. There was no residual urine. A cystogram showed a normal outline of the urinary bladder, and results of excretory urography appeared normal. A barium meal showed no connection between the small intestine and the umbilicus.

A persistent, draining subumbilical sinus appeared after the aspiration. Therefore, incision and drainage of the mass were performed. Indigo carmine was

inserted with the packings, but no dye appeared in the urine. A specimen removed from the cyst showed characteristic tuberculous granulation tissue, in which acid-fast bacilli were present. A second cystogram (fig. 2) now showed a sinus arising from the anterosuperior margin of the bladder, communicating with the anterior abdominal wall near the umbilicus. Urine began to seep rather freely from the wound. The course continued to be slowly downhill. Abdominal cramps were more frequent and more severe and were associated with vomiting. The abdomen gradually became more protuberant.

One month after admission visible peristalsis developed, pointing to obstruction of the bowel. Roentgen examination of the abdomen showed dilated loops of small intestine with fluid levels in the upright position. Evidence of increased peritoneal exudate was shown by separation of the intestinal loops. Laparotomy was

Fig. 2.—Cystogram, showing the urachus communicating with the anterior abdominal wall.

performed to relieve this obstruction, which was believed due to agglutination of intestinal loops by tuberculous peritonitis. The intestinal serosa was covered with many small tubercles, and the terminal portion of the ileum appeared to be involved for about 4 inches (10.2 cm.) by a tuberculous process. No intestinal adhesions were found. The patient died on the first postoperative day.

Anatomic Diagnosis.—At postmortem examination the anatomic diagnosis was as follows: mechanical ileus caused by incarceration of a loop of ileum in a ring produced by fibrous adhesion between the ileum and the rectosigmoid; generalized tuberculous peritonitis; ulcerative tuberculous jejunitis, ileitis, appendicitis and colitis; tuberculosis of mesenteric lymph nodes, with caseation; patent urachus, with tuberculous inflammation of the umbilical end of the duct; disseminated miliary tuberculosis of the lungs, liver and spleen; old caseated and calcified paratracheal and tracheobronchial lymph nodes.

Macroscopic Study.—Urachus: The abdomen was slightly distended and had a recent right rectus incision, 10 cm. in length, which was closed by Michel clips and had no evidence of infection. There was a triangular, dark red, granulating wound, 5 cm. in length, just below the umbilicus. A persisting, granulatnig urachus fistula extended into this wound from the anterior portion of the dome of the bladder. The entire tract was extraperitoneal, showing no communication with any part of the intestinal tract. The remainder of the bladder appeared normal except for tubercles on its peritoneal surface. One of the lymph nodes posterior to the bladder showed extensive caseation.

Peritoneal Cavity: The peritoneal cavity contained no free fluid. The peritoneal surfaces, including the inferior surface of the diaphragm, were studded with pea-

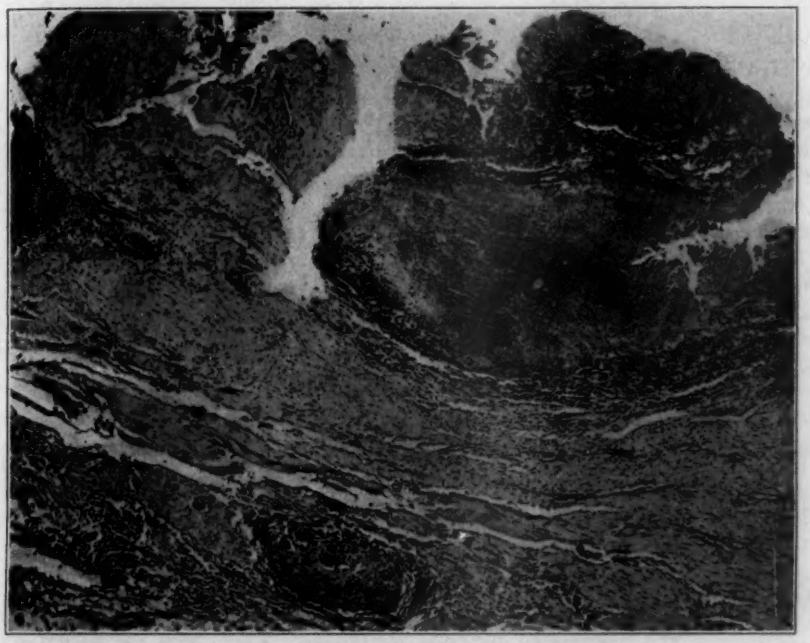

Fig. 3.—Section through the wall of the tuberculous urachus, showing extensive caseation.

sized, dark grayish yellow nodules. There were fibrous and fibrinous adhesions between the right lobe of the liver and the diaphragm. A strong fibrous adhesion between a loop of the ileum and the rectosigmoid had caused incarceration of a loop of the ileum. The loops of intestine proximal to the incarceration were distended, and those distal to the band were collapsed.

Intestinal Tract: The mucosa of the jejunum and ileum showed involvement in many regions by a grayish white pseudomembrane, which covered congested, grayish red areas. There were many elliptic serpiginous ulcers, which were transverse to the long axis of the small intestine. The ulcers had red, elevated edges and the centers were depressed, being covered with a similar pseudomembrane. There was no perforated ulcer. The wall of the terminal portion of the ileum was thickened, and its mucosa had a grayish, granular appearance. There were sinus tracts extending through the mucosa of the ileocecal valve. The appendix was

kinked by adhesions, and its mucosa was similar to that found in the terminal part of the ileum. The colon was less severely involved and had only a few ulcers. A deep round ulcer, the size of a ten cent piece, was situated in the rectosigmoid region, about which there was definite thickening of the wall of the intestine. The mesenteric lymph nodes were enlarged and firm, and many were matted together. Their cut surfaces had a grayish white, cellular appearance and showed yellow caseous foci but no calcification.

Lungs: The lungs contained patchy areas of atelectasis and edema. There was a solitary yellowish, caseated, subpleural nodule in the vertebral segment of the upper lobe of the right lung. Some of the paratracheal lymph nodes were 1 cm. in diameter and firm and on section showed yellow caseous and calcified areas surrounded by a firm, grayish white capsule.

Liver and Spleen: These organs contained a few scattered, pinhead-sized tubercles.

Histologic Study.—Microscopic examination revealed tuberculous inflammation of the umbilical end of the urachus, with caseation (fig. 3). The small intestine showed extensive tuberculous inflammation, involving the entire thickness of the wall in areas, and tuberculous mucosal ulcers; there were many tubercles on the peritoneum. The liver, spleen and lungs showed recent disseminated tubercles. The lungs had areas of atelectasis and edema, and the grossly visualized area of subpleural caseation was not calcified and was surrounded by dense fibrous tissue. The paratracheal lymph nodes showed extensive caseation, fibrosis and hyalinization. Areas of calcification were present, and there were recent tubercles in adjacent regions. Acid-fast bacilli were found in sections of the various organs.

COMMENT

This case is reported because of the unusual clinical manifestations and the rarity of reported cases of tuberculosis of a persistent urachus. The involvement of the urachus in this case was part of a generalized tuberculous infection. The urachus may have become infected by tubercle bacilli circulating within the body during the period of generalization. It cannot be denied, however, that, owing to the proximity of the extraperitoneal portion of the urachus to the area of tuberculous peritonitis, the passage of tubercle bacilli may have been permitted by direct extension through the lymphatics.

The intestinal tuberculosis must have been the result of transportation of bacilli by way of the blood stream and the lymph, because the site of primary tuberculous infection in the lung was encapsulated, was not in communication with a bronchus and showed no signs of activity.

SUMMARY

A case of tuberculosis of the urachus, the fourth to be described, is reported.

There was extensive tuberculosis of the intestines and peritoneum in this case but no evidence of involvement of any part of the genitourinary tract.

LEAD ENCEPHALOPATHY

TWO CASES, WITH A HYPOTHESIS OF THE BIOCHEMICAL PATHOGENESIS

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BROOKLYN

In 1932 Shelling suggested the use of a high phosphorus, low calcium diet in the therapy of acute plumbism. Since then several reports have appeared in the literature indicating the beneficial effect of a diet rich in phosphorus in the treatment of lead poisoning. In the pediatric service of the Jewish Hospital of Brooklyn, a number of patients with plumbism have been successfully treated by this means. Patients with mild and moderate lead encephalopathy have responded well. However, the mortality in children manifesting convulsions due to lead poisoning still remains high, because no satisfactory means of controlling the convulsions is yet known to medical science. Of 8 children with lead poisoning treated in the pediatric ward since 1932, 6 recovered, making a mortality of 25 per cent. All of the 8 manifested some symptoms of lead encephalopathy. The patients with mild encephalopathy were characterized by listlessness and irritability, those with moderate encephalopathy by vomiting and drowsiness and those with severe encephalopathy by convulsions. Five of the 8 manifested convulsions, and only 3 of these 5 recovered. The mortality, therefore, in cases of severe lead encephalopathy was 40 per cent.

In this paper, the 2 cases of fatal lead poisoning are reported. In both of these cases autopsies and analyses of the blood and tissues for lead were performed. It will be shown that the chemical [1] and anatomic [2] data obtained in these cases indicate that the essential disturbance of the brain is probably chemical. Further, an attempt will be made to throw light on what this chemical disturbance is and to derive from this hypothesis a therapy for severe lead encephalopathy.

REPORT OF CASES

CASE 1.—D. A., a white girl aged 18 months, was admitted to the pediatric service of the Jewish Hospital of Brooklyn on Nov. 23, 1937 because of con-

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From the Department of Pediatrics of the Jewish Hospital, Dr. Benjamin Kramer, Director.

1. A. E. Sobel and his staff, of the pediatric research laboratory and the division of biochemistry, Jewish Hospital of Brooklyn, made the chemical analyses.

2. M. Lederer and his staff, of the department of pathology of the Jewish Hospital of Brooklyn, made the postmortem anatomic studies.

vulsions of thirty minutes' duration. The family history was irrelevant. The history with respect to birth, feeding and development was normal. The patient was free of symptoms up to one week prior to the day of admission. At this time she became irritable and began to cry frequently for unusually long periods. A history of pica was not elicited. Convulsions appeared suddenly, on the morning of entry.

Physical Examination.—The patient was malnourished and pale. She was unconscious and frothing at the mouth. The right side of the mouth and the right upper extremity were twitching. Nystagmus of both eyes was present. There was no dyspnea or cyanosis. The circumference of the head was 51.5 cm. and that of the chest 45 cm., and the length was 77 cm. The weight was not obtained. The calvarium was larger than normal in proportion to the body. The anterior fontanel measured 2 by 2 fingerbreadths and did not bulge. The posterior fontanel was closed. The sutures were not separated. There was no craniotabes. The pupils of the eyes were equal and regular and reacted sluggishly to light. The fundi were normal except for pallor of the retinas. Examination of the nose, ears and throat revealed no pathologic condition. No lead line was present on the gums. The heart was normal, and the lungs were clear. The edge of the liver was palpable 4 cm. below the costal margin. Neurologic examination revealed no evidence of meningeal irritation. Deep and superficial reflexes were absent. All extremities were flaccid.

Course.—The patient died twenty-six hours after admission. The temperature, which was 98 F. at first, rose to 105 F. at the time of death. The convulsions failed to respond to repeated administrations of sedative drugs.

Laboratory Examinations.—Urinalysis showed the presence of 3.3 Gm. of dextrose [3] per hundred cubic centimeters, but the urine was otherwise normal.

Study of the blood showed that the hemoglobin content was 32 per cent; the red cells numbered 3,200,000 per cubic millimeter and the white cells 4,800, of which polymorphonuclears constituted 42 per cent, band forms 5 per cent and lymphocytes 53 per cent. A blood smear revealed increased central pallor of the red cells but no basophilic stippling. The Kline reaction of the blood was negative. Analysis of the blood serum showed the value for dextrose was 165 mg. per hundred cubic centimeters, for calcium 9.6 mg. and for phosphorus 4.3 mg. Analysis of whole blood showed 0.88 mg. of lead per hundred grams.

Spinal tap revealed a clear fluid under increased pressure, with a normal cell count. The Wassermann reaction of the spinal fluid was negative, and the colloidal gold curve was normal. Chemical analysis of the spinal fluid disclosed the value for calcium was 6.4 mg. per hundred cubic centimeters, for dextrose 91 mg., for chlorides 485 mg. and for total protein 85 mg. The qualitative reaction for globulin was positive.

Roentgen examination of the long bones revealed a line of increased density at the ends of the diaphyses. The roentgenogram of the skull showed no abnormality.

Analysis of bone (tibia) revealed 17.3 mg. of lead per hundred grams of dried bone. The brain contained 0.55 mg. of lead per hundred grams of dried tissue.

Autopsy.—The essential pathologic changes were limited to the brain. This organ weighed 1,345 Gm. The parietal lobes were bulging. The ventricles were

3. Because the patient died shortly after admission, positive identification of the reducing substance in the urine was not possible.

all slightly enlarged. Microscopic section taken through the region of the basal ganglions showed all blood vessels to be markedly distended and their walls thin. Many of those close to the lateral ventricles were surrounded by a dense collar of microglia. Nissl preparations of sections taken through various portions of the brain showed the neurons to be well preserved and in orderly arrangement.

CASE 2.—S. R., a white girl aged 28 months, was admitted to the pediatric service of the Jewish Hospital of Brooklyn on June 28, 1938 because of convulsions of three hours' duration. The family history was irrelevant. The history with respect to birth, feeding and development was normal. The patient had manifested pica for five months prior to admission. One month before entry she began to vomit after meals. Convulsions appeared in the morning of the day on which she was admitted.

Physical Examination.—The patient was pale and undernourished. She was semicomatose. There were twitchings of the face and of the left upper and lower extremities. The calvarium was normal in size and shape. The fontanels were closed. Lateral nystagmus of both eyes was present. The pupils were equal and reacted to light. Examination of the fundi disclosed bilateral papilledema and marked engorgement of the retinal veins. Examination of the ears, nose and throat revealed no pathologic condition. No lead line was present on the gums. The lungs were clear. The heart was normal except for tachycardia. Palpation of the abdomen revealed nothing pathologic. Neurologic examination failed to disclose any evidence of meningeal irritation.

Course.—The patient lived for only fifteen hours after admission to the hospital. The temperature, which was 98 F. at first, rose to 105 F. at the time of death. The convulsions failed to respond to repeated administration of sedative drugs, to ether anesthesia, to a 50 per cent solution of sucrose given intravenously, to several doses of 20 cc. of a 10 per cent solution of disodium hydrogen phosphate passed into the stomach by means of the Levin tube or to a 50 per cent solution of magnesium sulfate introduced intramuscularly.

Laboratory Examinations.—Urinalysis showed the presence of albumin (2 plus), but the urine was otherwise normal.

Study of the blood showed that the hemoglobin content was 63 per cent; the red cells numbered 3,600,000 and the white cells 36,000 per cubic millimeter. A differential count was not made. A blood smear revealed increased central pallor and basophilic stippling of the red cells. The Kline reaction of the blood was negative. Analysis of the blood serum showed the value for dextrose was 105 mg. per hundred cubic centimeters, for calcium 10.3 mg., for phosphorus 6.6 mg. and for phosphatase 9.1 Bodansky units. Analysis of the whole blood showed 0.58 mg. of lead per hundred grams.

Roentgen examination of the long bones revealed a line of increased density at the ends of the diaphyses. The roentgenogram of the skull showed no abnormality.

Analysis of the tissues for lead showed the value for striated muscle was 0.74 mg. per hundred grams of dried tissue, for spleen 10.7 mg., for cauda equina 0.65 mg., for cerebrum 2.01 mg., for liver 5.50 mg. and for kidney 2.04 mg.

Autopsy.—The lungs, liver, spleen and brain were affected. Microscopic study of both lungs revealed many small areas where polymorphonuclear leukocytes were present within the alveoli and interalveolar septums. These were especially numerous around some of the bronchioles. The epithelium of the bronchioles was

well preserved, and some of their lumens contained many polymorphonuclear leukocytes. A few of the alveoli of the left lung were filled with red blood corpuscles.

The liver measured 19 by 9.5 by 4.5 cm. and weighed 335 Gm. No arrangement of hepatic cell cords could be recognized in the microscopic sections. The sinuses were compressed, and the portal veins were distended. Almost all the hepatic cells contained a light-staining cytoplasm or small or large vacuoles.

The spleen measured 7 by 4 by 1.5 cm. and weighed 25 Gm. Sections taken through the spleen revealed necrotic areas in the germinal centers.

The brain weighed 1,225 Gm. The gyri were flattened and the sulci narrow. The pia-arachnoid was in many places opaque and somewhat thickened. The vessels over the hemispheres were markedly engorged. On study of a cross section of the brain, the lateral and third ventricles were found to be compressed and the blood vessels stood out prominently as red dots. Microscopic examination of various regions of the brain showed the essential pathologic changes to consist of: slight meningeal thickening, with round cell infiltration; congestion of blood vessels, with perivascular hemorrhages; increase of perivascular and pericellular spaces, with vacuolation, affecting chiefly the white matter; extensive chromatolysis of the neurons; acute swelling of the oligodendroglia cells and degenerative changes in the astrocytes; transformation of microglia into rod cells and compound granular corpuscles. The degenerative changes in the neurons were marked and varied from slight perinuclear chromatolysis to complete dissolution of the tigroid substance. The changes were generalized but affected the cells of the cerebral and cerebellar cortex to a greater extent than those of the brain stem. Considerable numbers of fat-filled phagocytes were present.

COMMENT

The chemical and anatomic data in these 2 cases bring to light several important facts. First, there seems to be no direct correlation between the level of lead in the blood and the degree of toxicity. The first patient had a concentration of lead in the blood of 0.88 mg. per hundred grams, while for the second child the value was 0.58 mg. Both of these children died in convulsions. However, in an earlier case of lead encephalopathy which I reported,[4] the concentration of lead in the blood was 0.72 mg. per hundred grams. The convulsions of this child were readily controlled, and the patient made a complete recovery. Second, there is no correlation between the level of lead in the blood and the structural deterioration of the brain. The first patient, who had the greater value for lead in the blood, showed no degeneration of the neurons in the brain, whereas the second patient, who had the lower value for lead, showed marked degeneration of the nerve cells. Third, there is a direct correspondence between the amount of lead in the brain and the degree of anatomic alteration. In the first case, in which the integrity of the neuronal structure was maintained, the lead content of the brain was 0.55 mg. per hundred grams

4. Kowaloff, I.: Lead Poisoning, Am. J. Dis. Child. **56**:764 (Oct.) 1938.

of dried tissue. In the second case, in which the structural deterioration of the neurons was severe, the lead content was 2.01 mg. Fourth, there is no correlation between the extent of the degenerative changes in the brain and the degree of toxicity. The poisoning in 2 cases was equally severe, yet in the first relatively little anatomic change was shown, whereas in the second a great deal of structural deterioration was revealed.

What conclusions can be drawn from these facts? The explanation for the symptoms of lead encephalopathy is probably to be found in conditions in the brain rather than in those in the blood. Since there is no correspondence between the extent of the anatomic change in the brain and the degree of toxicity, it appears that the primary pathologic change may be chemical rather than morphologic. The correlation between the lead content of the brain and the disintegration of the nerve cells seems to indicate that the morphologic changes of the brain are secondary to chemical disturbances induced by lead within the neuron.

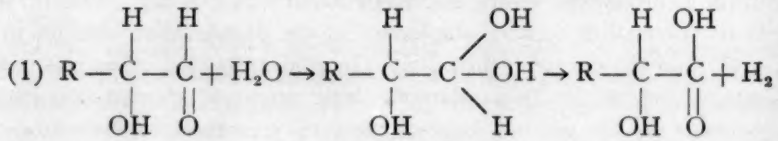
Enough is now known about the chemical events in the brain, the chemical properties of the organic phosphates and the biochemical behavior of lead to warrant the development of a hypothesis about the chemical pathologic changes in lead encephalopathy.

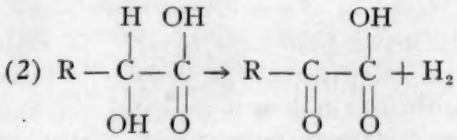
First, some of the facts known about the metabolism of the brain will be reviewed briefly. Glycolysis is one of the fundamental reactions taking place within the nerve cell. Glycolysis is a process in which the dextrose molecule is broken down into smaller and more reactive molecules. By condensation with each other and by combination with organic and inorganic compounds of nitrogen and phosphorus, the products of glycolysis give rise to practically all the organic molecules constituting the cell.[5] In the course of these many reactions carbon dioxide is set free and oxygen is consumed. This is summarized in the well known equation: $C_6H_{12}O_6 + 6\ O_2 \rightarrow 6\ H_2O + 6\ CO_2$ However, it must be emphasized that this equation merely indicates the beginning and the end of a series of oxidation-reduction reactions. The carbon is never directly oxidized in the cell to form carbon dioxide. In the generation of carbon dioxide from dextrose many intermediate products are formed. Some of these are lactic acid, pyruvic acid, methylglyoxal, acetaldehyde and glycerose. These compounds are derived from dextrose by three principal processes: (1) addition of water, (2) dehydrogenation and (3) splitting off of carbon dioxide.[6]

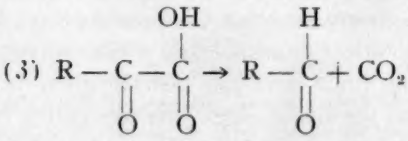
5. Mathews, A. P.: Physiological Chemistry, Baltimore, Williams & Wilkins Company, 1939.

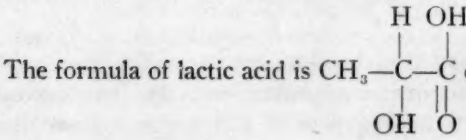
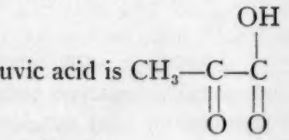
6. Barnes, J. C.: Textbook of General Physiology, Philadelphia, P. Blakiston's Son & Co., 1937.

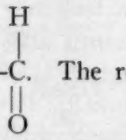
These reactions may be represented schematically as follows:







The formula of lactic acid is  of pyruvic acid is 

and of acetaldehyde is  . The relation of these compounds to each other is readily seen by referring to the schema given. In the process of biologic oxidation, water and hydrogen thus assume the principal roles. Oxygen serves as a hydrogen acceptor. It unites with hydrogen to form water after the molecule derived from glycolysis has already been oxidized by dehydrogenation.

All these biologic reactions are speeded up by enzymes, or organic catalysts. Thiamine and nicotinic acid have been found in recent investigations to be important constituents of these enzymes.[5] Thiamine is a part of the enzyme molecule known as cocarboxylase, which is able to decarboxylize pyruvic acid to form acetaldehyde and carbon dioxide. Nicotinic acid is a part of the enzyme molecules called cozymase (coenzyme I) and coenzyme II. These catalysts are codehydrogenases and function by virtue of the reversible power of hydrogenation and dehydration of the nicotinic acid radical.

This brings up one of the most important points concerning glycolysis, namely, the role of phosphoric acid.[5] Before glycolysis can occur, the esterification of dextrose with phosphoric acid to form a monophosphoric or diphosphoric acid ester of dextrose must first take place. This phosphorylation of dextrose is mediated by the nicotinic acid

enzymes. Moreover, it appears likely that both thiamine [7] and nicotinic acid [8] must first be conjugated with phosphoric acid before they can play their part as catalysts in the glycolytic reactions. Thus, thiamine reacts with phosphoric acid to form the ester of pyrophosphoric acid, and nicotinic acid is conjugated with phosphoric acid and other substances to form diphosphonucleotide and triphosphonucleotide. Thiamine pyrophosphate is known as cocarboxylase. The nucleotides are, respectively, coenzyme I and coenzyme II.

Finally, some important results of recent investigations in the biochemical behavior of lead should be indicated. In a previous paper [4] I suggested that the principle of the solubility product with respect to lead phosphate was possibly the determining factor in the reciprocal relation between the lead in the whole blood and the serum phosphorus in a clinical case of lead poisoning. Further, Sobel, Yuska, Peters and Kramer [9] indicated that in the rat the solubility product principle with respect to lead phosphate might be the governing factor in the deposition of lead in bone and in the absorption of lead from the gastrointestinal tract into the blood.

The hypothesis that I now wish to introduce is that lead, acting in accordance with the solubility product principle with respect to lead phosphate, produces the symptoms of lead encephalopathy by interfering with the normal chemical reactions occurring in the neuron. The lead is toxic to the brain because it inhibits the synthesis of organic phosphates and thereby prevents glycolysis.

A discussion of the theoretic basis for this hypothesis follows:

The formation of an organic phosphate is a reversible reaction. The monophosphate of dextrose will illustrate this. If the hexose phosphate is represented by $R(H_2PO_4)$ and the free hexose by ROH, then:

(4) $R(H_2PO_4) + H_2O \rightleftarrows ROH + H_3PO_4$

The ionization of lead phosphate and that of phosphoric acid are likewise reversible reactions:

(5) $Pb_3(PO_4) \rightleftarrows 3Pb^{++} + 2PO_4^{\equiv}$

(6) $H_3PO_4 \rightleftarrows 3H^{+} + PO_4^{\equiv}$

According to the solubility product principle,

(7) $[Pb^{++}]^3 \times [PO_4^{\equiv}]^2 = K_1$

7. Williams, R. R.: The Chemistry of Thiamin (Vitamin B_1), in The Vitamins: A Symposium, Chicago, American Medical Association, 1939, chap. 7, pp. 141-158.

8. Sebrell, W. H.: Vitamins in Relation to the Prevention and Treatment of Pellagra, in The Vitamins: A Symposium, Chicago, American Medical Association, 1939, chap. 16, pp. 297-321.

9. Sobel, A. E.; Yuska, H.; Peters, D. D., and Kramer, B.: The Biochemical Behavior of Lead, J. Biol. Chem. **132**:239 (Jan.) 1940.

According to the law of chemical equilibrium,

$$(8)\ \frac{[H^+]^3 \times [PO_4^{\equiv}]}{[H_3PO_4]} = K_2 \text{ and}$$

$$(9)\ \frac{[ROH] \times [H_3PO_4]}{[R(H_2PO_4)] \times [H_2O]} = K_3$$

In these equations, the brackets represent the concentration in moles per liter. K_1 is the solubility product constant of lead phosphate. K_2 is the ionization constant of phosphoric acid. K_3 is the equilibrium constant of the reversible chemical reaction indicated by equation 4. From equation 7 it is seen that an increase in the concentration of lead ion will cause a depression of phosphate. According to equation 8, a decrease in the concentration of phosphate ion will result in a diminution of phosphoric acid. According to equation 9, a decrease in the concentration of phosphoric acid will be associated with a decrease of hexose phosphate and an increase of free hexose. The effect of an increase in the concentration of lead, therefore, is to shift the point of equilibrium, so that hydrolysis of organic phosphate is favored at the expense of the synthesis of organic phosphate.

What are the consequences of this action of lead? Glycolysis must be inhibited, because the phosphorylation of dextrose, of thiamine and of the nicotinic acid complexes is prevented.

Experimental evidence for the deduction that lead inhibits the synthesis of organic phosphate already exists. Steiman [10] showed that in the voluntary muscle of a normal animal phosphocreatine hydrolyzed during a two minute period of tetanus was completely resynthesized after a half hour period of recovery. In the case of animals poisoned with lead there was practically no resynthesis of the phosphocreatine hydrolyzed during a two minute period of tetanus of striated muscle.

There is also experimental evidence for the deduction that glycolysis is inhibited by lead. Dolowitz, Fazekas and Himwich [11] showed that lead influenced brain tissue by interfering with the utilization of dextrose and lactic acid, by reducing the oxygen consumption and by abolishing dehydrogenation.

If the principle of the solubility product and the law of chemical equilibrium determine the action of lead on the brain, the behavior of calcium in nervous tissue should be similar to that of lead, since calcium, like lead, forms a difficultly soluble salt with phosphate. This appears to be the case. Chang, Shaffer and Gerard [12] showed that the addition

10. Steiman, S. E.: The Action of Lead on Phosphocreatine in the Muscular Paralysis of Lead Poisoning, Am. J. Physiol. **126**:261 (June) 1939.

11. Dolowitz, D.; Fazekas, J. F., and Himwich, H. E.: The Effect of Lead on Tissue Metabolism, J. Indust. Hyg. & Toxicol. **19**:93 (Feb.) 1937.

12. Chang, T. H.; Shaffer, M., and Gerard, R. W.: The Influence of Electrolytes on Respiration in Nerve, Am. J. Physiol. **111**:681 (April) 1935.

of calcium ion to physiologic solution of sodium chloride in which nerve tissues were immersed resulted in a decrease in the oxygen consumption of the neurons. When graded concentrations of calcium ion were used, respiration decreased as the concentration of calcium increased. On the other hand, the addition of salts the anions of which form difficultly soluble compounds with calcium, such as sodium citrate, sodium oxalate and sodium phosphate, resulted in an immediate increase in the oxygen consumption of the neurons. The greater the concentration of oxalate or phosphate added, the lower became the concentration of calcium and the greater became the volume of oxygen consumed. Such biochemical behavior on the part of calcium in nerve tissue indicates that the administration of an excessive amount of calcium without an equivalent amount of phosphorus to a patient with acute lead poisoning will have a disastrous effect.

That lead acts in the brain cell in accordance with the solubility product principle with respect to lead phosphate appears, therefore, quite possible. A rational therapy for severe lead encephalopathy can now be deduced. If lead interferes with the synthesis of organic phosphates, it would be a reasonable procedure to supply the brain with dextrose and vitamins already phosphorylated. Intravenous administration of dextrose phosphate, thiamine hydrochloride pyrophosphate ester and nicotinic acid may be the solution to the problem of the control of the severe convulsions of lead encephalopathy. For not only would these substances restore the glycolytic reactions in the brain, but the inorganic phosphate liberated on hydrolysis of the excess hexose phosphate would serve to decrease the concentration of lead ion in the nerve cell. However, such therapy would not be effective in patients in whom severe structural deterioration of the nerve cells had already occurred. Thus, the first patient reported on in this paper might have responded to this treatment, whereas the second would not.

SUMMARY

Two cases of lead encephalopathy are presented in which analyses for lead and anatomic studies of the tissues were made.

No direct correlation between the level of lead in the blood and the degree of toxicity was found.

A direct correspondence between the lead content of the brain and the extent of the degenerative changes of the brain was noted.

There was no correlation between the degree of structural deterioration of the brain and the degree of toxicity.

It is concluded that the primary pathologic change in lead encephalopathy is probably a chemical disturbance induced by lead within the nerve cell.

A summary of the present knowledge of metabolism of the brain and the biochemical behavior of lead is given.

The hypothesis is presented that lead acts in the brain in accordance with the solubility product principle with respect to lead phosphate and that by inhibiting phosphorylation it interferes with the metabolism of the brain.

Experimental evidence for this hypothesis is cited.

The intravenous administration of dextrose phosphate, thiamine hydrochloride pyrophosphate ester and nicotinic acid is suggested as a rational means of controlling the severe convulsions of lead encephalopathy.

STURGE-WEBER SYNDROME

ITS OCCURRENCE IN TWO CASES

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Recently, O'Brien and Porter [1] reviewed the literature on the Sturge-Weber syndrome. They found records of 55 cases over a period of seventy-two years and to these added a case of their own. Subsequently, Nussey and Miller,[2] in 1939, found 145 cases (mostly European) reported in the available literature and described another case. Bentsen and his associates,[3] published a study of the syndrome, and Pincus [4] and Newson [5] have each reported a case. Observations on an increasing number of patients have revised the conception of the pathogenesis of this disease.

A patient with this syndrome has vascular nevi, usually along the course of the superior and middle branches of the trigeminal nerve, glaucoma of the eye on the same side and vascular nevi of the pia. Various other conditions may be present, such as intracranial calcification, pituitary dystrophy, hemiatrophy of the brain, with calcification (mostly in the occipital and temporal lobes on the same side as the angioma), atrophy of the side of the body opposite to that with the angioma, paralysis, aphasia, anosmia, jacksonian epilepsy and mental retardation. Difficulty in resuscitation immediately after birth has been described in various reports. Most patients usually have more than one of the conditions mentioned. In 1933, O'Brien and Porter stated that a nevus or angioma of the meninges was usually present. The

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From the Departments of Contagious Diseases and Ophthalmology of the Cleveland City Hospital and the Departments of Pediatrics and Ophthalmology of the Western Reserve University School of Medicine.

1. O'Brien, C. S., and Porter, W. C.: Glaucoma and Naevus Flammeus, Arch. Ophth. **9**:715-728 (May) 1933.

2. Nussey, A. M., and Miller, H. H.: Sturge's Disease, Brit. M. J. **1**:822-823, 1939.

3. Bentsen, K. G.; Dalsgaard-Nielsen, E., and Möller, H. U.: Study of Sturge-Weber Syndrome, Particularly from the Standpoint of Ophthalmologic Symptoms, Acta ophth. **16**:279-294, 1938.

4. Pincus, M. H.: Naevus Flammeus Associated with Glaucoma, Arch. Ophth. **21**:741-745 (May) 1939.

5. Newson, A. L.: Case of Sturge's Disease, Brit. M. J. **2**:1088, 1939.

evidence from recent gross and microscopic studies reveals that the sine qua non of the Sturge-Weber syndrome is the pial nevus.

Two patients with this disorder were admitted to the division of contagious diseases, Cleveland City Hospital, to the service of Dr. John A. Toomey. The observations on these patients serve to illustrate two stages of the syndrome.

REPORT OF CASES

CASE 1.—J. T., a white girl aged 2½ months, was first seen in the eye clinic of the outpatient department, Cleveland City Hospital, on Nov. 18, 1939. Two days later she was admitted to the hospital with the tentative diagnosis of pertussis. The chief complaints were bulging and clouding of the left eye and cough.

Fig. 1 (case 1).—J. T., showing the "oxeye" with steamy cornea and naevus flammeus over the left side of the face.

History.—The baby was born at Cleveland City Hospital; the delivery was normal and at full term. There was no difficulty in resuscitation at birth. The neonatal period was uneventful. The infant was fed breast milk, supplemented with cow's milk, and an adequate amount of vitamins. Her development was normal. At birth there was naevus flammeus on the left side of the face corresponding to the distribution of the superior and middle branches of the trigeminal nerve. There was also buphthalmos on the same side. No other abnormality was noted.

Physical Examination.—Examination on admission to the hospital showed a well developed and well nourished child. The respiratory and pulse rates and the temperature were normal. The head was normal in shape. A nevus covered the cheek and the frontal and periorbital areas on the left side (fig. 1). Several small nevi were found on the mucous membrane of the mouth on the left side. The right eye was normal. The intraocular pressure was 14 mg. of mercury

(Schiötz). The left eye was prominent and enlarged (fig. 2). The cornea measured 14 mm. in diameter. The conjunctiva and the sclera were mildly inflamed; the cornea was hazy and the iris blue. The fundus could not be visualized because of edema of the cornea. The movements were apparently normal. The anterior chamber was deep, and the pupillary reaction was normal.

Body Measurements.—The occipitofrontal circumference of the head was 38 cm. The anterior fontanel was about 3 cm. in diameter and the posterior fontanel was closed. The bisacromial circumference was 39 cm., the abdominal circumference at the umbilicus 37 cm., the iliac circumference 32 cm. and the length of each arm 18 cm. The distance from the anterior superior spine of the ilium to the external malleolus of the left leg was 24 cm.; on the right side it was 24.5 cm. The distance from the symphysis pubis to the top of the head was 34.5 cm. and from the symphysis pubis to the heel 21.5 cm.

Laboratory Data.—All blood counts and examinations of the urine gave normal results. The concentration of calcium in the blood was 11.5 mg. per hundred cubic centimeters, of inorganic phosphorus 7.5 mg., of phosphatase 16.8 mg. and of cholesterol 132 mg. The Kline reaction of the blood was negative. Roentgen examination of the cranial vault gave normal results.

CASE 2.—S. J., a 12 year old white boy, was admitted to the hospital on Oct. 5, 1939, because of erysipelas of the left leg.

History.—The patient was born at Cleveland City Hospital at full term; delivery was accomplished by means of low traction forceps. He was thought to be a "blue" baby and had some trouble in starting to breathe. He was breast fed for two months and then put on a diet of cow's milk, orange juice and cod liver oil. He received diphtheria toxoid at the age of 9 months and was vaccinated against smallpox when 6 years of age.

At 16 months of age he had a severe attack of pertussis. About the sixth week of this disease he suddenly had a convulsion, which lasted for seven hours, after which he was found to be completely paralyzed on the right side. Three days later he was taken to a hospital, where a diagnosis of pontile hemorrhage, buphthalmos, healed rickets and hydrocephalus was made. There was a marked increase in the pressure of the spinal fluid, but there was no evidence of block nor were pathologic cellular elements present. Two weeks after his discharge from this hospital he was admitted to another institution, where a diagnosis of cerebral hemorrhage on the left side, congenital cutaneous lesions and congenital hydrocephalus was made. Examination of the spinal fluid at this institution also gave negative results.

Since then, he has been in various hospitals for the orthopedic correction of various deformities caused by the paresis of his right side. At the age of 4, the report of a roentgen examination in one hospital read: "Films of the skull show it to be asymmetric. There is a marked increased bulge in the right parietal region. The left parietal bone is markedly thickened, measuring 15 mm. in width. The width of the skull bones of a patient of this age should measure 5 or 6 mm. The frontal and occipital bones are also thicker than normal. Despite this thickening the inner and outer contours of the bones appear to be normal. The sutures can be well visualized and their ossification appears to be approximately normal. The sella turcica is of normal size for a patient of this age. The sphenoid sinuses are not developed as yet. The patient has an asymmetrically thick skull, which could be due to congenital anomaly or to some internal secretory disturbance."

The child had varicella at 2 and measles at 2½ years of age. He was operated on for correction of a congenital inguinal hernia at the age of 4.

Present Illness.—On Oct. 3, 1939, the patient fell and sustained a small abrasion of the left leg. The next day he had a chill, with fever and general malaise. On October 5 he began to have pain and erythema of the left leg, and a diagnosis of erysipelas was made.

Family History.—There was no history of any previous occurrence of the Sturge-Weber syndrome in the family.

Examination.—The mental development was retarded. The general development was asymmetric, the right arm and leg being smaller than his left. Multiple port wine nevi were scattered over the body, chiefly over the upper parts of the arms, the thighs, the upper part of the trunk and the face. The distribution on

Fig. 2 (case 2).—J. S., showing distribution of the facial nevus, hemiatrophy of the face and buphthalmos.

the face did not definitely follow the course of the superior branch of the fifth nerve. There was a fine maculopapular eruption over the abdomen and the lower part of the chest. On the medial aspect of the left leg was an abrasion of the skin, with a surrounding red area of inflammation. Old surgical scars were present on the right arm and in the right inguinal area. The cervical and left inguinal lymph nodes were enlarged and tender. The head was asymmetric, the left side being smaller than the right.

Both eyes seemed larger than normal. The cornea of the right eye measured 12 mm.; the sclera appeared to be thin, with patches of uveal pigment showing through (fig. 3). The scleral vessels were slightly dilated and tortuous, with small deposits of pigment along their course. The cornea was clear and the anterior chamber deep (fig. 4). The pupil reacted to light. The fundus was

Fig. 3 (case 2).—Eyeball rotated downward, showing pigmented areas of uvea showing through the thin sclera and circoid dilatation of scleral blood vessels.

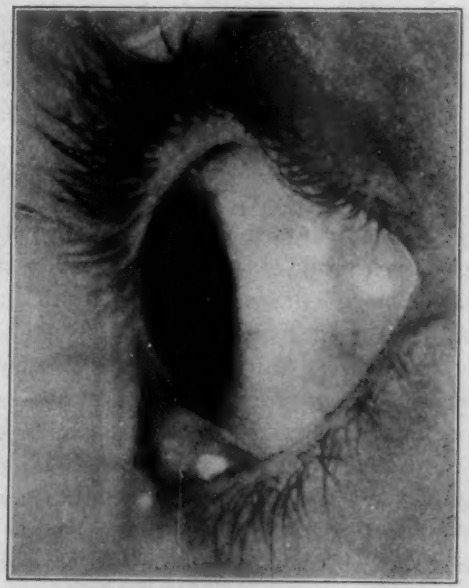

Fig. 4 (case 2).—Lateral view of buphthalmic eye, showing depth of the anterior chamber.

heavily pigmented. The disk and vessels appeared normal. Intraocular tension (Schiötz) was 26 mm. of mercury. The left eye was larger than the right and had a clear cornea, measuring 13.5 mm. in diameter. The scleral vessels around the limbus were circoid, and surrounding them were small deposits of pigment. Several large areas of pigmentation were seen in the sclera. The anterior chamber was deep. The pupil reacted to light. The fundus was heavily pigmented. The optic disk was white and deeply evacuated. The intraocular tension was 48 mm. of mercury (Schiötz).

Both inferior turbinates of the nose were injected and enlarged. The pharynx was red, and there were some small follicular exudates on the tonsils.

There was adiposogenital dystrophy. The testes were in the scrotum, and the penis was small.

The diameters of the arm, forearm, leg and thigh on the right were smaller than those of the corresponding extremities on the left. The right leg was slightly shorter than the left. The right extremities were weaker than the left. The right hand was held partly clenched, and the fingers could not be extended. The right foot was fixed in hyperextension. The reflexes were normal.

Laboratory Data.—The results of blood counts, determinations of hemoglobin levels and urinalyses were normal. The concentration of calcium in the blood was 12.1 mg. per hundred cubic centimeters, of phosphorus 5.6 mg., and of cholesterol 180 mg. The dextrose tolerance curve showed a blood sugar level of 89 mg. per hundred cubic centimeters during fasting, 130 mg. one-half hour after ingestion of dextrose, 86 mg. after one hour, 93 mg. after two hours and 75 mg. after three hours. The blood cultures were sterile. The basal metabolic rate was + 17 per cent. The Kline reaction was negative. A roentgenogram of the skull showed no intracranial calcification. The sella turcica was normal.

Diagnosis.—The diagnosis was: scarlatina (questionable); cellulitis of the left leg, with inguinal lymphadenitis; erysipelas (questionable); multiple port wine nevi, and Sturge-Weber syndrome.

COMMENT

In the Sturge-Weber syndrome there is a congenital anomaly of the vessels of the pia, choroid and skin, thus an anomaly essentially mesodermal in origin. Though the structures in which the lesions occur are widely separated later in life, the angioma of the choroid of the eye and the common involvement of the skin in the distribution of the first and second branches of the trigeminal nerve and of the pia overlying the occipital and temporal lobes on the same side can be easily explained by the proximity of these structures during fetal development. It has been suggested by Peters [6] that the anomaly starts before the fifth fetal month. Scheinker [7] quoted Penfield as expressing the belief that the disease was hereditary. This was not the case in our patients. The

6. Peters, G.: Pathogenesis of Sturge-Weber's Disease, Ztschr. f. d. ges. Neurol. u. Psychiat. **164**:365-379, 1939.

7. Scheinker, I.: Clinical Aspects, Pathology and Pathogenesis of Sturge-Weber Syndrome: Contribution to Histogenesis of So-Called Angioglioma; Case, Ztschr. f. d. ges. Neurol. u. Psychiat. **163**:604-616, 1938.

theories of the causation of the glaucoma have been summarized too well by O'Brien to be detailed here.

Peters [6] examined tissues from 3 patients microscopically and was able to demonstrate a progression of changes in the central nervous system with different age levels. His patients were 15 months, 8 years and 32 years old. Scheinker reported studies on a patient 54 years old.

In Scheinker's patient and in the oldest patient of Peters, the gross and microscopic observations showed varying degrees of vascularity of the pia overlying atrophied tissue, the occipital and temporal lobes of the brain being most frequently affected. The well vascularized leptomeninges had the appearance of a hematoma, but closer observation showed the presence of many tortuous and dilated vessels. The tissue of the brain beneath the angioma was atropic and infiltrated with deposits of calcium. The calcification was chiefly about the vessels, but deposits were found independently in the brain substance. The brain cut with increased resistance, and the cortex felt sandy, the degree of these characteristics being dependent on the amount of calcification. The pons and medulla were reduced in size.

Microscopically, the occipital and temporal lobes were studded with calcium deposits, the largest being in the second and the upper part of the third layer of the cerebral cortex. In the fifth and sixth layers there were droplet-like deposits and concretions which seemed to lie free in the tissue, although some looked like small calcified vessels. The white matter was decreased and contained some calcified small vessels. There was a marked decrease in the cells of the second and third layers of the occipital lobe on the affected side. In the neighborhood of the larger calcium deposits, the ganglion cells were atrophic and there was a great deal of glial proliferation. Large protoplasmic astrocytes were observed in all layers. There was some degeneration, since granular fat cells were found in the cortex, a few in the white matter and some along the vessels. The blood vessels of the overlying pia were tortuous and made up of a single layer of endothelial cells supported by a thin collagenous layer.

In the youngest of Peters' patients there were only pial nevi and droplet-like deposits of calcium in the cortex; the latter were not anywhere near the size of those seen in the adult brains.

The neurologic manifestations are bizarre and are due either to atrophy or to aplasia of the brain underlying the angiomatous pia. Peters [6] concluded that the condition is probably atrophy, since neurologic symptoms rarely appear before the age of 2 years and since microscopic studies at all ages show all six layers of the cerebral cortex to be present.

The 2 patients reported on in this paper presented stages in this chronic progressive disease. The first, an infant, demonstrated only

buphthalmos and a nevus; the second, a 12 year old child, presented nearly all the neurologic changes of this disease reported in the literature.

Nussey and Miller [2] expressed the belief that this syndrome may be confused with jacksonian epilepsy and advised roentgen examination of the skull in all cases in which the presence of the syndrome is suspected.

CONCLUSION

Observations on 2 patients with the Sturge-Weber syndrome have been presented. Emphasis has been placed on the primary importance of the presence of the pial nevus in identifying this disease.

OSSEOUS ATROPHY ASSOCIATED WITH PROGRESSIVE MUSCULAR DYSTROPHY

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While there are many references to skeletal deformities (anomalies of size and shape of the skull, funnel-shaped chest, kyphoscoliosis and deformities of the pelvis and foot [1]) in the vast literature on progressive muscular dystrophy, comparatively few papers have dealt with the osseous atrophy found in association with this muscular disease.

On the other hand, some of the authors (Curschman,[2] Jendrassik [1]) who alluded to such an association claimed that osseous atrophy is not an infrequent accompaniment of muscular dystrophy. This osseous atrophy at first thought appears to be a secondary process, a disuse phenomenon due to muscular inactivity. Such an assumption, however, is not justified in the face of arguments advanced by authoritative writers.

As early as 1873, the subject was given a discussion a chapter in length in Friedreich's [3] monograph on muscular dystrophy. He reported a case of his own and cited an earlier similar observation of Le Gendre,[4] an observation which, according to Friedreich, was the first on record to show the occurrence of osseous atrophy in a verified (post mortem) case of progressive muscular dystrophy. The protocol of the autopsy in Friedreich's case (that of an 18 year old youth) describes, aside from the characteristic microscopic and macroscopic features of dystrophic muscle, marked changes in the osseous system. Along with certain skeletal deformities (large cranial roof, scoliosis and a poorly developed, abnormally tilted pelvis), there was atrophy of varying degree of most of the skeletal bones: clavicles, scapulas, ribs, innominate bones and all long

1. Jendrassik, E.: Dystrophia musculorum, in Lewandowsky, M. H.: Handbuch der Neurologie, Berlin, Julius Springer, 1911, vol. 2, p. 345.

2. Curschman, H.: Dystrophia musculorum progressiva, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 16, p. 431.

3. Friedreich, N.: Ueber progressive Muskelatrophie, über wahre und falsche Muskelhypertrophie, Berlin, A. Hirschwald, 1873, pp. 344-351.

4. Le Gendre, cited by Friedreich.[3]

bones. The last, though of normal length, had strikingly thin diaphyses. For instance, the circumference of the femurs was hardly that of the little fingers. Also atrophied, but to a lesser degree, were the epiphyses of the long bones. The articular cartilages of the bones of the extremities were atrophic and "sunken" in certain areas. A study of a longitudinal section of an atrophied long bone revealed an extremely narrow medullary cavity. However, the proportion of the thickness of the cortex to the width of the marrow cavity remained the same as that seen in normal bone. To explain this phenomenon, Friedreich postulated that with the "external, concentric, progressive bone atrophy" there was a simultaneous deposition of new bone along the medullary surface of the cortex; an identical process was assumed for the flat bones, since the spongeous spaces were found to be either extremely narrow or completely obliterated. Friedreich argued that the normal length of the long bones, the disappearance of the cancellous layer in some of the flat bones and the patchy atrophy of articular cartilages indicated a regressive nutritional process, an atrophy, rather than an arrest in development or a standstill in the growth of bone. Further, he discarded disuse as a cause of the osseous atrophy, arguing that often enough one finds no osseous atrophy in cases of the most advanced muscular dystrophy. Nor, in his opinion, could the changes in articular cartilages and the marked atrophy of ribs and iliac bones be accounted for by lack of activity of wasted muscles. Friedreich concluded with the assumption that some disturbance in the vasomotor centers in the central nervous system may be responsible for osseous atrophy in the course of muscular dystrophy.

A significant contribution to the subject was Eulenburg's [5] publication (1896) of a case of "infantile familial muscular dystrophy" in a 15 year old boy whose 3 brothers, 17, 12 and 8 years of age, and 10 year old sister had some indications of the same muscular disease. The patient's osseous system showed hypertrophic and atrophic changes. Roentgenograms of the right shoulder revealed thickening and considerable elongation of the clavicle and hypertrophy of the head of the humerus. A roentgenogram of the right hand showed mild hypertrophic changes in the metacarpal bones and basal phalanges and more pronounced hypertrophy of the phalangeal epiphyses. Contrasted with this hypertrophy were the narrowing of the sternum and thinning of the ribs. It is noteworthy that in the 12 year old sibling there were osseous changes in the hands similar to those found in his next oldest brother.

5. Eulenburg, A.: Ueber einen schweren Fall infantiler, familiärer Muskeldystrophie mit osteo-arthropathischen Deformationen, Deutsche med. Wchnschr. **22**:458, 1896.

Two years later Schultze [6] reported on the incidence of osseous atrophy in 2 siblings, only 1 of whom, a 10 year old boy, had "familial progressive muscular pseudohypertrophy," [7] while the other, a sister, had *spondylose rhizomélique* (spondylitis deformans). Postmortem study of the male sibling revealed changes in the osseous system similar to those already described by Le Gendre and by Friedreich. For instance, the femur, though of normal length, had a thickness equal to that of the middle finger. The humerus was even thinner; its normal-appearing cortex made up the greater part of the structure, leaving only a narrow medullary cavity. In this patient, too, the ribs were thin, the pelvis small and the vertebral column kyphoscoliotic. The picture of osseous atrophy in the sister was essentially similar to that in her myopathic brother, although she was free from any indication of muscular dystrophy. This case, by its implication, served Schultze as further evidence that Friedreich's "concentric" osseous atrophy (Schultze suggested the name "bone dystrophy") was a process not dependent on muscular dystrophy. He expressed the belief, however, that these two conditions have the same cause and that this cause is a hereditary predisposition to trophic changes in the muscular and osseous systems.

In 1903, Marie and Crouzon [8] reported a case of etiologically undetermined fracture of the humerus in a boy with "progressive myopathy." Roentgenograms revealed that the involved bone had a diameter almost equal to that of the middle finger of a normal man. These writers expressed the belief that the osseous atrophy was of the type described by Le Gendre, Friedreich and Schultze and assumed that in the presence of possibly increased fragility of the bone muscular action or a minor trauma might have caused the fracture.

In 1905, Schlippe [9] reported a case of "marked contractures and skeletal atrophy associated with progressive muscular dystrophy" in a 19 year old boy, whose younger brother had the same muscular disease. The paper has received widespread attention, since it contains the first detailed roentgenologic account of osseous atrophy in association with muscular dystrophy. The roentgenograms revealed that the vertebral column and ribs were gracile, that the long bones of the upper

6. Schultze, F. R.: Ueber Combination von familiärer progressiver Pseudohypertrophie der Muskeln mit Knochenatrophie und von Knochenatrophie mit der Spondylose rhizomélique bei zwei Geschwestern (mit Sectionsbefund in einem der Fälle), Deutsche Ztschr. f. Nervenh. **14**:459, 1898-1899.

7. Schultze labeled the form of muscular dystrophy in this case "familial" because of the history of a similar muscular disease in an older brother who had died.

8. Marie, P., and Crouzon, V.: Un cas de fracture par atrophie osseuse de l'humérus chez un myopathique, Rev. neurol. **11**:239, 1903.

9. Schlippe, P. L.: Hochgradige Kontrakturen und Skelettatrophie bei Dystrophia musculorum progressiva, Deutsche Ztschr. f. Nervenh. **30**:128, 1905-1906.

and lower extremities, though of normal length, showed extreme reduction in the diameter of their diaphyses and that this small circumference of the long bones was due more to the narrowness of the medullary canal than to a reduction in the thickness of the substantia compacta, an observation already made by Friedreich and by Schultze. In contrast to the slender diaphyses, the epiphyses appeared disproportionately large. The cancellous tissue of the scapulas no longer appeared as a "uniform, rather dense shadow" but had a "light, weblike structure," due to rarefaction of the fine trabeculae with preservation of the coarser ones. In the cancellous tissue of the long bones there were similar changes: the characteristic picture of the lines of force was missing, and in its place only a wide-meshed spongy structure was discernible. Such an alteration was especially conspicuous in the bones of the feet. The light shadows cast by the vertebral column and ribs indicated that these bones also had not escaped the process of rarefaction.

A year or so later, Dreyer [10] described almost identical roentgenographic observations in 2 siblings with muscular dystrophy. Both Schlippe and Dreyer shared Schultze's view concerning the nature of osseous atrophy in muscular dystrophy.

Merle and Raulot-Lapointe,[11] in 1909, reported the result of roentgenographic study of the skeletal system in 7 cases of muscular dystrophy. The diaphyses presented a characteristic appearance in their extreme thinness and transparency, so that their roentgen images resembled "transparent, thin glass tubes." The trabeculae and lines of force in the epiphyses were no longer visible. In some instances the compact tissue in the patella had completely disappeared (*rotule de verre*). Changes in the form of the bones were equally distinctive. Since the thinness of the diaphyses was greatest in the portions adjoining the epiphyses, the long bones appeared dumbbell shaped.

The authors admitted that bones are apt to undergo alterations secondary to muscular atrophy, but roentgenographic examination of the bones in the earlier stages of the disease conveyed to them the impression that the muscles and bones were involved in a parallel manner under the action of a common cause. They concluded that the osseous changes should not be considered as secondary, that there is not only progressive myopathy but also progressive osteopathy (progressive osteomyopathy).

Jendrassik [1] (1911), in his discussion of osseous atrophy associated with muscular dystrophy, accepted Schultze's designation "bone dystrophy" as a term indicating the primary nature of the process.

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10. Dreyer, L.: Ueber Skelettveränderungen und Frühkontrakturen bei Dystrophia musculorum progressiva, Deutsche Ztschr. f. Nervenh. **31**:147, 1906.

11. Merle, P., and Raulot-Lapointe: Les altérations osseuses au cours de la myopathie, Rev. neurol. **17**:385, 1909.

Weight is added to the theory of the idiopathic character of the osseous atrophy by Curschman's [2] recent statement that he often failed to find such atrophy in cases of advanced muscular dystrophy studied roentgenologically.

The literature in English contains little which has a direct bearing on the subject. Lloyd,[12] in 1884, described interesting osseous changes in a 17 year old girl with progressive hypertrophic muscular dystrophy. He found atrophy of the patellas, which had no more than half the normal diameter, and a "preternatural mobility" of the larger joints of the upper extremities. For instance, the elbow joint could be bent backward to a marked degree, and there were "wabbling and limberness" in pronation and supination. He assumed that atrophy of the epiphyses and loosening of the joint ligaments were responsible for the hypermobility of the articulation.

In 1905, Spiller [13] described a case of the Landouzy-Déjerine type of muscular dystrophy with osseous atrophy, the latter not affecting the length of the long bones. In an earlier paper he [14] had already assumed that "a process which causes atrophy and arrest in the development of muscles, beginning in early life, probably involves the bones as well."

A similar opinion was expressed by Goodhart,[15] who stated:

> . . . in view of our findings of definite pathologic changes in structures other than muscles, especially the skeletal, we may reasonably conclude that the muscular anomalies are but a part of a more general pathologic participation.

Endocrine disturbances were considered by him and his collaborators [16] as the possible etiologic basis of this more general pathologic change in the primary myopathies. Bramwell,[17] however, expressed the belief that changes in bone and muscle in muscular dystrophy ". . . may perhaps be determined by disease of the sympathetic supply."

The case reported here is representative of osseous atrophy in muscular dystrophy. The scarcity of publications in the American literature describing similar cases justifies, we believe, this report.

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12. Lloyd, T. H.: The Report of a Case of Pseudo-Hypertrophic Muscular Paralysis with Bone Lesions, J. Nerv. & Ment. Dis. **2**:627, 1884.

13. Spiller, W. G.: Atrophy of Bone in Progressive Muscular Dystrophy, Rev. Neurol. & Psychiat. **3**:388, 1905.

14. Spiller, W. G.: A Case of Progressive Muscular Dystrophy (Landouzy-Déjerine Type), with Microscopical Examination of the Sternocleidomastoid Muscle, M. Rec. **54**:9, 1898.

15. Goodhart, S. P.: The Primary Myopathies and Their Endocrine Relationship, M. Clin. North America **2**:259, 1918.

16. Janney, N. W.; Goodhart, S. P., and Isaacson, V. I.: Endocrine Origin of Muscular Dystrophy, Arch. Int. Med. **21**:188 (Feb.) 1918.

17. Bramwell, E.: The Muscular Dystrophies, Sympathetic System and Endocrine Glands, Lancet **2**:1103, 1925.

REPORT OF A CASE [18]

J. P., a 16 year old Italian boy, was admitted to the Central and Neurological Hospital Jan. 26, 1937. He had been transferred from the New York Hospital, with a diagnosis of progressive muscular dystrophy.

The patient was the fifth youngest sibling in a family in which no similar muscular disease was known. He started to walk at the age of 14 months, and until the onset of the present illness neither clumsiness nor abnormal fatigue marked his childhood activities. With the exception of measles and chickenpox at the age of 6, there was nothing of importance in the patient's past history.

At the age of 8, he complained of weakness in his legs and arms. When he was about 9 years old, he frequently fell on his knees and had considerable difficulty in getting up ("climbed up on his legs"). At 11, when his muscular weakness had progressed to such a degree that he was unable to walk down steps, he was hospitalized. His short stays at Bellevue Hospital (three months) and at Metropolitan Hospital (two months) were followed by transfer to St. Agnes Hospital July 21, 1931, where he remained for about fifteen months.

During the entire period of hospitalization his condition grew steadily worse, so that he finally lost the ability to stand or walk; however, he could still use his arms and even raise them above his head. After his discharge from St. Agnes Hospital he was cared for at home, where the muscular weakness in the upper extremities soon progressed to the point of total inability to execute any movements involving the shoulder and elbow joints. On Oct. 15, 1936, he was admitted to the New York Hospital, where special metabolic studies were conducted by Dr. A. T. Milhorat.

Physical Examination.—The patient was confined to bed, practically unable to execute any active movements using the larger joints, and at first glance one was more impressed with the skeletal deformities than with the muscular wasting. In a sitting position, there were marked dorsal scoliosis and prominent dorsolumbar lordosis. In a prone position, the trunk was arched and turned to the right, the thighs and legs were externally rotated, the feet were in the equinovarus position and there was bilateral pes cavus. An interesting anomaly was the failure of the teeth to occlude properly (fig. 1). When the jaws were approximated, only the molar teeth came in contact, so that a large oval space remained between the rest of the upper and lower teeth. On inspection, no abnormalities in size and shape of the head were noted; the length of the trunk and extremities appeared to be normal.

There was a mild flexion contracture at the elbow joints (the forearms could be passively extended to an angle of 150 degrees). The patient could not actively extend or flex his forearms; however, he could perform these movements by a climbing motion with his fingers along the wall of the chest. The patient was unable to execute any active movements involving the shoulder joints, but marked hypotonia allowed complete freedom of passive motion. Active movements of the wrists and fingers were not impaired. Both thighs were in flexion contracture, permitting passive extension only to an angle of 120 degrees; active movements were still more limited. A similar flexion contracture of the knee joints allowed passive extension of the left leg to an angle of 130 degrees and of the right leg to an angle of 150 degrees. Active movements, however, were

18. The patient in the case reported in this paper was studied at the Central and Neurological Hospital, Welfare Island, New York.

not possible. There was a plantar flexion contracture at both ankle joints; active movements in these joints were considerably limited, while the range of passive motion was appreciably greater. The patient could move his toes freely.

The musculature showed features of advanced dystrophy. The shoulder, arm, forearm, small muscles of the hands and muscles of the back and thigh were markedly atrophic; the gluteal, gastrocnemius and peroneal muscles were obviously hypertrophic and of a hard, fibrous consistency. Considering that the patient could extend his head but could not flex it, there must have been involvement of at least some of the muscles of the neck. Electrical examination of the muscles showed no reaction of degeneration, while their mechanical irritability was lost in all except the facial group.

Deep reflexes in the upper and lower extremities could not be elicited; superficial reflexes were brisk. Superficial and deep sensation were normal. There was no disturbance in the function of the cranial nerves. The fundi were normal.

Fig. 1.—Malocclusion of the teeth. Note the short vertical ramus and the obtuse angle of the mandible.

The mental status was normal. The intelligence quotient was 98 (Stanford-Binet standard, 1937 revision).

Examination also showed macroglossia, overdeveloped external genitalia and tapering fingers. The heart and lungs were normal; the blood pressure was 124 systolic and 90 diastolic. The liver and spleen were not palpable.

Roentgen Examination.—The skull showed moderate exostosis of the internal portion of the frontal bone. The mandible had a short vertical ramus and obtuse angle (fig. 1), and the following measurements were obtained: vertical ramus, 6.2 cm.; body, 9.5 cm.; gonion angle, 133 degrees. (The method of measurement used was that described by Zabriskie, Hare and Harris.[19] The average measure-

19. Zabriskie, E. G.; Hare, C. C., and Harris, M. M.: Progressive Muscular Dystrophy: A Group of Five Cases Presenting Some Peculiar Deformities, Bull. Neurol. Inst. New York **5**:526, 1936.

ments for 12 normal subjects reported by them were: vertical ramus, 6.6 cm.; body, 8.6 cm.; gonion angle, 126 degrees.)

In the scapulas there was diffuse decalcification of the inner structure. The vertebral column showed gracile thoracic vertebrae. The ribs were thin. The pelvis was of the female type (wide, rounded inlet; gracile bones); the upper portions of the iliac bones showed diffuse decalcification of the inner structure.

The heads of the humeri (fig. 2 *A*) were of almost normal size and out of proportion to the extreme thinness of the shafts (dumbbell shaped); the cortex of the diaphyses was slightly reduced in thickness; the medullary canal was diminished

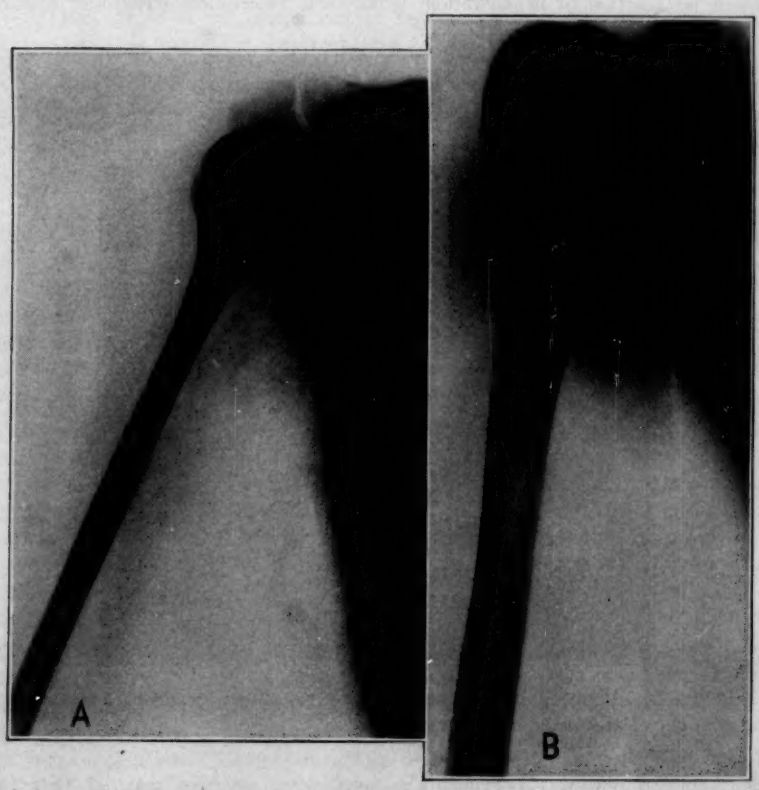

Fig. 2.—*A*, the extremely thinned shaft of the humerus of the patient. *B*, shaft of the humerus of a healthy boy of the same age as the patient.

to about one half of normal. The contour of the elbow joints and the architecture of the bones entering these joints were normal. The bones of the forearms showed marked thinness, due mainly to a decrease in the caliber of the medulla. The metacarpal bones were definitely diminished in diameter, owing to narrowing of the medullary canal.

The caliber of the shafts of the femurs was obviously diminished. There was considerable osteoporosis in the knee joints, in the condylar region of both femurs and in portions proximal to the epiphysial line; there was poor visualization of the normal "lines of force" and disappearance of the finer trabeculae. The contour of all bones entering the knee joints was normal; the patellas and upper

ends of the fibulas showed mild diminution in density. In the tibias and fibulas there was considerable reduction of normal thickness, mainly at the expense of the medullary cavity (fig. 3). In the bones of the feet there was extensive rarefaction, most marked in the calcaneus, where there was almost complete disappearance of the normal architecture (fig. 4).

Report of Biopsy (Dr. I. M. Tarlov and Dr. J. Rosenthal).—The specimen of muscle was taken from the right peroneal group. The report follows:

"The muscle is very pale, and there is considerable fat. Microscopic examination reveals that the specimen consists of muscle fiber tissue and considerable

Figure 3

Figure 4

Fig. 3.—Tibia and fibula, showing reduced thickness.

Fig. 4.—Extensive rarefaction in metatarsal bones, especially in the calcaneus.

fat, which has intruded itself among muscle bundles and individual fibers. The muscle fibers vary considerably in size and show degenerative formations, varying from loss of striation to complete fragmentation. In some areas there seems to have been proliferation of sarcolemmal nuclei with replacement of muscle fibers by connective tissue. The pathologic diagnosis is Myopathy, primary."

Laboratory Data.—Results of study of blood cell types, examination of the spinal fluid, dextrose tolerance test and chemical determinations on the blood were all normal. The calcium-phosphorus ratio was 10.8: 3.1. The creatin-creatinine

determinations showed creatinuria, decreased excretion of creatinine and low creatin tolerance. The Wassermann reactions of the blood and spinal fluid were negative. The basal metabolic rate was —7 per cent. The electrocardiogram was normal.

COMMENT

The symptoms of the case reported here are a combination of three clinical features: muscular dystrophy, marked contractures involving most of the larger joints and osseous changes.

The diagnosis of muscular dystrophy was firmly established by biopsy. A rather unusual feature in this case of muscular dystrophy is the involvement of the small muscles of the hands. However, there are cases of unquestionable dystrophy on record in the neurologic literature in which a similar occurrence was presented (Erb,[20] Zimmerlin [21] and others).

Contractures are not uncommon in progressive muscular dystrophy. Some writers still believe that such contractures invariably owe their origin to the continuous hypertonic state of the nonaffected antagonistic muscles. While it is true that such a mechanism holds for so-called paralytic contractures (caused by lesions of the pyramidal tract), as well as for some of the contractures occurring in the earlier stages of muscular dystrophy, contractures appearing late in the same disease are given an entirely different explanation by most investigators.[22] They have expressed the belief that in the course of the disease the atrophic muscle undergoes gradual shrinkage due to fibrosis, and it is this shrinkage, or retraction, of the muscles and tendons that ultimately leads to a permanent fixation of the joint involved (for example, talipes equinovarus). "Pseudocontracture" is the name suggested for this phenomenon. Clinically, such a contracture is characterized by freedom of movement in the joint to a point beyond which neither active nor passive movements are possible. Our case clearly illustrates this point.

However, it is the osseous changes which are the most striking in this case. Roentgenologic study revealed extraordinary thinness of the long bones, gracile pelvic bones, thin ribs, marked rarefaction of many of the bones and a short vertical ramus of the lower jaw, with an obtuse mandibular angle. Since no pathologic changes were found in the temporomandibular joint itself and since the muscles producing mandibular movements were not involved in the dystrophy, it can be safely stated that the deformity of the lower jaw does not represent a disuse phenomenon; and it is this that renders the observation significant. The mandibular deformity seems not to be a mere coincidence.

20. Erb, cited by Schlippe.[9]

21. Zimmerlin, cited by Schlippe.[9]

22. For a review of the literature the reader is referred to the papers of Jendrassik [1] and Schlippe.[9]

Zabriskie, Hare and Harris [19] recently published their observations in 5 cases of muscular dystrophy, in each of which was exhibited a triad of clinical signs consisting of contractures involving the larger joints, pseudohypertrophy of the anterior tibial muscle group and deformity of the mandible, "which exhibits a very wide angle, a malocclusion of the front teeth and a wide spacing of the lower teeth." Localized hypodevelopment of the vertical rami of the inferior maxilla was suggested by them as an explanation for this type of mandibular malocclusion. An earlier observation of such malocclusion was reported by Kollarits.[23]

The osseous change which appeared to us most interesting was the "concentric" osseous atrophy.

The relatively slight reduction of the thickness of the cortex as compared with the extreme thinness of the shaft of the long bones presupposes that the reduction in the diameter of such bones is mostly at the expense of the medullary canal. Indeed, in our own case and in cases reported by others, marked reduction in the caliber of the medullary canal was found. We are not prepared to say whether a compensatory deposition of new bone along the medullary surface of the long bones and in the spongeous spaces of the flat bones takes place, as Friedreich claimed. In this connection, however, it is interesting to note that Virchow [24] found evidence of such a process in the senile atrophy of flat bones.

This osseous atrophy did not impress us as a phenomenon due to muscular inactivity. The normal length of the atrophied long bones and atrophy of bones which could hardly be affected by muscular disuse (ribs and pelvic bones) would speak against the dependence of osseous atrophy on muscular dystrophy. The thinness of the metacarpal bones in the face of unimpaired activity of the fingers may serve as an additional argument against the secondary nature of the concentric osseous atrophy. Furthermore, the reader will recall that Curschman often failed to find osseous atrophy in cases of advanced muscular dystrophy. Finally, a cogent argument is Eulenburg's case of muscular dystrophy, in which both osseous atrophy and hypertrophy were found. It seems more reasonable that the changes in bone and muscle in muscular dystrophy are independent processes brought about by the same cause, whatever it may be—an endocrine disorder or, as Kuré and his pupils [25] have suggested, a disturbance of the vegetative nervous system.

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23. Kollarits, J.: Beiträge zur Kenntnis der vererbten Nervenkrankheiten, Deutsche Ztschr. f. Nervenh. **30**:293, 1905-1906.

24. Virchow, cited by Friedreich.[3]

25. Kuré, K.; Okinaka, S., and Ohshima, K.: Vier Sektionsfälle von Dystrophia musculorum progressiva mit besonderer Berücksichtigung des autonomen Systems, Ztschr. f. d. ges. Neurol. u. Psychiat. **155**:157, 1936.

In conclusion, we should like to suggest that roentgenologic studies be undertaken in early stages of progressive muscular dystrophy in which muscular activity is not yet appreciably impaired. Should the already described osseous changes be found, further convincing evidence would be adduced against disuse as the cause of the "concentric" osseous atrophy.

SUMMARY

A case of progressive muscular dystrophy with extensive osseous atrophy is described. The literature on the subject is reviewed.

The arguments advanced by authoritative writers and the analysis of the case presented here lead us to believe that the characteristic osseous atrophy associated with progressive muscular dystrophy is not a phenomenon of disuse.

Dr. D. E. Ehrlich carried out the roentgen studies, and Edna Simon, M.A., administered the psychometric test.

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Progress in Pediatrics

PRIMARY TUBERCULOUS INFECTIONS IN YOUNG ADULT LIFE AND IN CHILDHOOD

WITH REFERENCE TO THEIR RELATIVE ADVANTAGES AND DISADVANTAGES

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When the physicians who are middle aged today studied medicine, they were taught that tuberculous infection was so widespread that every one who reached childhood had already been infected. Nowadays medical students are taught something quite different; that hardly 50 per cent of all children have a positive reaction to tuberculin and that it is not until after the age of puberty that the majority of persons gradually become infected. This difference in doctrine does not imply that the former conception was wrong. A change in the age at which primary infection occurs has undoubtedly taken place. This can be proved for certain by comparing the results of tuberculin tests done by the same method and on children of the same social groups at intervals of two or three decades. The results of two comparable investigations conducted at the Children's Clinic in Vienna are often cited. Some thirty years ago (1909) Hamburger and Monti [1] reported that all of the children whom they examined at the age of 15 years had been infected with tuberculosis. Applying the same method (intracutaneous testing with up to 1 mg. of tuberculin) Dietrich,[2] one of Hamburger's own pupils, reported in 1937 that hardly half of the children examined at the same age had been infected. There is every reason to believe that a similar decline in the number of primary infections in childhood and a corresponding increase of infection in the adult period have taken place in all civilized countries.

The question now arises whether this postponement of the primary infection to a later period of life is to be regarded as an advantage or a disadvantage. Formerly it was considered advantageous if the primary infection was acquired in childhood because of its immunizing effect. This immunity was believed to be of importance in preventing severe pulmonary processes if the person was exposed to infection later in life.

From the Medical Department of the Children's Hospital.

1. Hamburger, F., and Monti, R.: Die Tuberkulosehäufigkeit im Kindesalter, München. med. Wchnschr. **56**:449, 1909.

2. Dietrich, A.: Ueber die Tuberkulosehäufigkeit im Kindesalter, Med. Klin. **33**:1637, 1937.

Nowadays some authors (Myers and Harrington [3] and Stewart [4]) go so far as to assert that infection in childhood is altogether disadvantageous in that it favors rather than arrests the development of serious forms of tuberculosis in the adult.

In judging the advantages or disadvantages of infection during childhood over primary infection acquired in the adult period, regard must be paid, on the one hand, to the immediate effects of primary infection and, on the other hand, to the appearance of postprimary tuberculous diseases, especially pulmonary tuberculosis.

There are two immediate results of a fresh primary infection, one unfavorable and the other favorable. The undesirable effect is the development of pathologic changes in proximity to the primary complex. The favorable effect of a primary infection is the specific immunity against tuberculosis which it confers. Whether the hypersensitivity established at the same time is advantageous or disadvantageous is a more difficult matter to make clear in a few words. I believe that it can be both an advantage and a disadvantage, according to the nature of the particular case. As a rule, if the hypersensitivity is pronounced, it probably should be regarded as an undesirable phenomenon. In general, however, hypersensitivity is hardly as great a disadvantage as immunity is an advantage.

Immunity against an infectious disease is a valuable acquisition. The earlier tuberculous immunity is established, the longer will be the time during which the person can benefit from it. As is well known, tuberculous immunity is relative in two respects. In the first place, it can be broken down by severe reinfections. This has been demonstrated by animal experiments, and it is certainly also true in the case of human beings. It is not certain, however, whether natural aerogenous or enterogenous reinfections can be severe enough to break down a specific immunity. That is at any rate a doubtful eventuality (Lange [5]), which involves too many factors to discuss in this connection. Immunity against tuberculosis is also relative in another respect: It seems to imply exclusively, or mainly, an increased specific resistance to exogenous reinfections; it can do little or nothing to nullify the effect of the pathogenic activity of tubercle bacilli already present in the body.[6]

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3. Myers, J. A., and Harrington, F. E.: The Effect of Initial Tuberculous Infection on Subsequent Tuberculous Lesions, J. A. M. A. **103**:1530 (Nov. 17) 1934.

4. Stewart, C. A.: Does a Primary Tuberculous Infection Afford Adequate Protection Against Consumption? J. A. M. A. **100**:1077 (April 8) 1933.

5. Lange, B.: Quellen, Wege und Eintrittspforten der kindlichen Tuberkuloseinfektion, in Engel, S., and Pirquet, C.: Handbuch der Tuberkulose, Leipzig, Georg Thieme, 1930, vol. 1, p. 113.

6. Wallgren, A.: From Childhood Infection to Adult Type of Pulmonary Tuberculosis, Acta tuberc. Scandinav. **10**:321, 1936; Pulmonary Tuberculosis in Children, in Miller, J. A., and Wallgren, A.: Pulmonary Tuberculosis in Adults and Children, New York, Thomas Nelson & Sons, 1939, p. 113.

The immunity to tuberculosis is established and perhaps at its height when the primary infection manifests itself. No one has seen exogenous superinfections develop during this period. Nevertheless, in many cases this acquired immunity not only fails to arrest the spread of the tubercle bacilli of the primary complex but is incapable of preventing them from having pathogenic effects on the endogenously infected organs, which may result, among other things, in the development of miliary tuberculosis and tuberculous meningitis. During the six months or so after immunity against tuberculosis has been manifested and is still high, it is incapable, for instance, of preventing the development of tuberculous pleurisy in about 25 per cent of the hospitalized children with erythema nodosum who have had a tuberculous infection. Later it cannot prevent the manifestation of postprimary tuberculosis, such as in the bones and joints, the urogenital tract and, especially, the lungs. That such manifestations occur, and frequently, cannot at any rate be interpreted as an expression of an effective immunity against the tubercle bacilli which are active within the organism.

It is possible that the immunity is ineffective against endogenous tubercle bacilli because it is only relative immunity; it offers little or no protection against the frequently heavy endogenous infections, while on the other hand it affords, practically speaking, absolute protection against the usually weak, natural, aerogenous superinfections. In practice, the effect is the same as if the immunity was directed only against exogenous bacilli, or in all events the infected person seems to have no other advantage from this specific immunity. As is well known, the case of syphilis is analogous: An exogenous syphilitic reinfection cannot take place, while the already existing infection may progress and may even lead to a fatal outcome.

Even if the immunity acquired affords only an increased resistance to exogenous tuberculous superinfections, great value must be ascribed to it. If two groups of persons, only one of which is immune, are exposed to tuberculous infection, the members of the immune group are much more favorably situated than those of the other group because the generally mild exogenous superinfection usually has no influence on their general health. On the other hand, the same mild infection may produce serious primary and early secondary forms of tuberculosis in many of the members of the nonimmune group. Moreover, the exogenous infection may be acquired under especially unfavorable conditions, such as during pregnancy, shortly after childbirth or after an attack of a resistance-reducing disease, such as measles, influenza or whooping cough, in which case there is a still greater risk of progression of the tuberculous infection. Without doubt the specific immunity, even if it is to a great extent relative, must be regarded as a distinct advantage and a valuable asset.

The undesirable effect of a primary infection is related to the anatomic changes which arise at the location of the primary complex. Until a few decades ago these sequelae were only known to occur in childhood, for obvious reasons. Few primary infections occurring in the adult period were detected during their period of manifestation, and the picture of disease was then frequently misinterpreted. Today it is known not only that the same tuberculous infection, called primary tuberculosis, occurs in adults but that it may have the same malignant course at that period of life as it sometimes has in childhood. Thus a primary infection may be associated with certain immediate risks no matter at what age it occurs. All physicians specializing in the treatment of tuberculosis undoubtedly agree on that point. The question still being debated is whether the degree of risk is greater or smaller in the one age period or the other.

In comparing the prognoses of primary infections at different ages it is of importance that the cases, from the tuberculosis point of view, be comparable. For one thing, the tuberculous infection must be of the

TABLE 1.—*Interval Between the Manifestation of Primary Tuberculosis and Meningitis*

Interval, months.....	0 to 1	1 to 2	2 to 3	3 to 4	4 to 5	5 to 6	6 to 7	7 to 13	Total
Number of cases.....	15	25	12	4	2	3	2	1	64

same age, either recent or of long standing, in both cases. For instance, the case of a 1 year old child with a primary infection which is still in its febrile initial stage cannot be compared with that of another 1 year old child in which the primary infection took place six months or more previously. The latter child is in a much more favorable situation than the former. The reason that their cases cannot be compared is that the danger threatening the newly infected person is enormously greater during the first months after the manifestation of the infection than later. This danger proceeds, at least in children, only to a small extent from the tuberculosis of the primary complex itself; this seldom progresses sufficiently to cause death. The danger comes from the early postprimary infections: meningitis and miliary tuberculosis.

The decrease in the risk of contracting these diseases with the lapse of a few months is illustrated by table 1. The table is based on data from cases in which the time of the onset of the infection or of the manifestation of the primary tuberculosis was known exactly. In these cases meningitis was the disease which followed the primary tuberculosis. It is much more difficult to obtain reliable data on the time of onset of miliary tuberculosis because the clinical symptoms may appear a long time after the anatomic manifestations of the disease. There is no doubt,

however, that miliary tuberculosis behaves in the same manner as meningitis. The features of those cases in which exact data have been obtained by means of continuous, careful roentgen examination correspond exactly with those in cases of meningitis.

Thus the first three months after the manifestation of the primary infection constitute the period of risk. As a rule, the prognosis for an infected person who has passed through this dangerous period is good, while the immediate prognosis for a person who is in the middle of this period is dubious.

The extent of the risk that early, malignant postprimary tuberculous diseases will develop, however, is also linked to the age at which the primary infection is manifested. The younger the infected person, the greater the risk. This is seen clearly in the well known age curve for meningitis, which shows that this disease is especially common during the first three years of life, although the total number of children infected with tuberculosis is lowest during that period. This appears also from

TABLE 2.—*Death Rate from Primary Tuberculosis During Childhood and Youth*

	Age, Years				
	0 to 1	1 to 3	3 to 7	7 to 16	Young Adults
Number infected	39	64	225	125	507
Percentage of deaths	36.9	15.6	4.4	0.8	0.79

table 2, which shows the death rate from primary tuberculosis in the different age periods of childhood and youth. The table includes only patients observed from the onset of the initial fever; that is, the children were kept under continuous control from the beginning of the primary tuberculosis. From the table it will be seen that 37 per cent of the children primarily infected during the first year of life succumbed and that the death rate fell rapidly to a minimum of 0.8 per cent during school age. From these data the conclusions may be drawn that if a tuberculous infection during childhood cannot be avoided everything possible must be done to prevent its occurring during the first year of life. As far as primary tuberculosis and the early postprimary tuberculous diseases are concerned, infection during the first years of life must be regarded as an absolute disadvantage.

When comparing the advantages and disadvantages between childhood infection and infection in young adult life, one therefore does not need to include infections in the first years of life for consideration. There can be no doubt that a primary infection in infancy is always attended with much more serious risks of the occurrence of malignant primary and early postprimary tuberculous diseases than an infection acquired in any other age period. I shall comment later on the ques-

tion of tertiary tuberculosis. The only point that admits of discussion is the prognosis for a primary tuberculous infection which takes place in young adult life as compared with the prognosis when infection occurs during school age.

Unfortunately, I lack adequate material on infections in adults for comparison. I have assembled data from different sources which show the death rate from primary infection among groups of young adults, such as students, conscripts and probationary nurses. The primary data are taken from the works of Heimbeck,[7] Scheel,[8] Malmros and Hedvall,[9] Holm and Helweg-Larsen,[10] Arborelius,[11] Kristensson[12] and Myers.[13] In all instances the persons studied were under observation while the tuberculin reaction changed from negative to positive. The total number of primarily infected adults for whom data are included in the reports in question was 507, of which 4 (0.79 per cent) died from primary or early postprimary tuberculous conditions associated with the manifestation of primary tuberculosis. Phthisis will be dealt with later.

If these figures are compared with the mortality rate given in table 2 for patients infected during school age, no difference can be found in the prognoses for the primary infections in young adults and for those in school children. It is possible, perhaps probable, that the prognosis for primary infection is more favorable for members of the still older age groups, but I do not possess any definite evidence on that point. With the data at present available one cannot demonstrate an advantage or a disadvantage, a better or an immediately worse prognosis for the primary infection which takes place in school age as compared with that occurring in young adult life, if the problem is considered solely from a medical point of view.

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7. Heimbeck, J.: Tuberculosis in Hospital Nurses, Tubercle **18**:97, 1936; personal communication to the author.

8. Scheel, O.: Primo-infection tuberculeuse de l'adolescent et de l'adulte, in Rapports de la dixième Conference de l'Union internationale contre la tuberculose, Lisbon, 1937, p. 213.

9. Malmros, H., and Hedvall, E.: Studien über die Entstehung und Entwicklung der Lungentuberkulose, Leipzig, Johann Ambrosius Barth, 1938.

10. Holm, J., and Helweg-Larsen, P.: Three Years of Investigation on Tuberculosis Among Medical Students at University of Copenhagen, Ugesk. f. læger **100**:118, 1938.

11. Arborelius, M.: Klinische Studien über die Tuberkuloseinfektion bei Erwachsenen, besonders mit Hinsicht auf das Vorkommen von Primäraffektionen, Acta Soc. med. suec. **56**:115, 1930.

12. Kristensson, A.: Zur Kenntnis der Tuberkulosefrequenz beim weiblichen Krankenpflegepersonal, Acta tuberc. Scandinav. **6**:117, 1932; Zur Kenntnis der tuberkulösen Infektion bei Krankenpflege-Elevinnen, ibid. **7**:1, 1933.

13. Myers, J. A.: Relation of First Infection to Clinical Tuberculosis, Am. J. Dis. Child. **59**:1385 (June) 1940.

A different conclusion can of course be drawn if instead one studies and tries to estimate the frequency of tertiary pulmonary tuberculosis when primary infection takes place in childhood in comparison to its frequency when such infection takes place in adult life. The question is then: Is phthisis more likely to develop in those persons infected during childhood or in those infected during young adult life, or is the risk equally great for the persons in both categories?

For the occurrence of tertiary pulmonary tuberculosis a number of different factors in addition to tuberculous infection are of importance, such as heredity, unfavorable living conditions, physical strains tending to reduce the power of resistance and, according to some authors,[6] exogenous superinfections. One must at least pay attention to the factors mentioned when comparing two groups of patients, one group composed of persons infected in childhood and the other of persons infected in adult life. Great caution must be exercised to avoid making mistakes in one direction or the other. In the follow-up studies made thus far the difficulties encountered were not overcome. The basic material was such that generalizations could not be formulated on the basis of the results of the investigation, for the data were not applicable to other groups of human beings. Another point worthy of attention is the varying conception as to what is to be regarded as tertiary pulmonary tuberculosis. All investigators are agreed, I suppose, that primary pulmoglandular tuberculosis does not come under this heading, but opinions differ with regard to other forms of tuberculosis of the lungs. Those cases which Malmros and Hedvall,[9] for instance, regarded as instances of manifest, though incipient, phthisis will not be recognized by every one as examples of the first stage of pulmonary tuberculosis.

In fact, no follow-up examination has been carried out with regard to the relative frequencies of pulmonary tuberculosis among persons infected in childhood and those infected in young adult life. It is exceedingly difficult to collect for study a group of people from each category which will satisfy all the requirements and thus insure that the results of a follow-up investigation will be significant. To mention only a few of these conditions, I may point out that the members of both groups should be of the same age and that they should have passed the age of predilection for phthisis; that is, they should be at least 30 years old. They should belong to the same stratum of the population and should live under similar economic, social and hygienic conditions. The proportion of females in the two groups should be equal, and their heredity should be similar. The same criteria for the diagnosis of pulmonary tuberculosis should be applied to the two groups. The period of observation should not be too short.

Two examples will illustrate the importance of observing these precautions. If regard is paid exclusively to the age at which primary infection takes place, a comparison made between a group of persons infected in childhood and another group that has reached young adult age without being infected does not take into account the fact that the former group must contain a much larger number of persons belonging to tuberculous families, that is, persons with a tuberculous heredity, than the latter group. In making a comparative study of two groups of probationary nurses, one composed of girls who had been infected in childhood and the other of girls infected during the period of probationership, one should not overlook the fact that those infected in childhood have already passed through the first period of risk, which, with all its hazards, the newly infected have yet to pass through, and that the probationary nurses are in the middle of the predilection age of phthisis and, moreover, are living under unfavorable conditions (herded together, obliged to stand long vigils, etc.), which in themselves predispose to pulmonary tuberculosis.

It would be only natural that a follow-up investigation of the first kind would show a higher incidence of phthisis among those infected in childhood and equally naturally, that an investigation of the second type would indicate a high frequency of phthisis among those infected in adult life. As a rule, a plausible explanation can be found for the divergence of opinion met in the literature with regard to the incidence of pulmonary tuberculosis among persons infected in childhood and among those infected in adult life. The results of the individual investigations are doubtless correct in themselves, but they do not permit of generalizations, nor was it suggested by the respective investigators that they do. But when these works are cited by others, more evidential force is frequently ascribed to them than is warranted. It is certain that proof has not yet been brought forth that infection in childhood in itself is more conducive or less conducive to the subsequent development of tertiary pulmonary tuberculosis than is a primary infection contracted in young adult life.

On purely theoretic grounds it appears rather an advantage to pass through puberty and adolescence with a well healed, immunizing childhood infection behind one. It can hardly be a chance occurrence that at present, when primary infections are acquired so frequently after childhood, one observes that acute pulmonary tuberculosis develops in so many young people, who, so far as can be judged, have been newly infected. Such observations were doubtless the reason that primary infection in adults was chosen as the subject of discussion at the tenth conference of the International Union Against Tuberculosis, at Lisbon, Portugal, in 1937. It seems probable and reasonable that pulmonary

tuberculosis will develop more readily in conjunction with a fresh, perhaps fairly large, progressive primary tuberculous focus in the lungs than in conjunction with an old, inactive, and perhaps calcified, primary complex acquired in childhood. It is well known that even the latter type of lesion may flare up in young adult life under the influence of certain internal and external factors, which are frequently unknown. However, there are reasons for assuming that the tendency to progression is greater while the tuberculous process in the lung is still active after a fresh primary infection. My own belief is that the age period in which the infection is acquired, provided it does not occur during puberty or young adult life, when the risk of phthisis is greater, does not play a dominant role in the incidence of pulmonary tuberculosis. Other factors are undoubtedly of more importance.

In view of the facts previously mentioned, I do not wish to attach any special importance to statistical data, but I should like to point out that according to the follow-up studies made by Frölich,[14] Herlitz,[15] Myers [16] and others in 4 to 7 per cent of the persons infected in childhood tertiary pulmonary tuberculosis developed. In a follow-up investigation made twenty-five years ago on children who had had tuberculous cervical lymphomas, I [17] found that in 10 per cent pulmonary tuberculosis had developed when they reached the predilection age of phthisis. By way of comparison I may refer to the data from the published series of cases previously mentioned in connection with the incidence of infection in young adult life: Of 507 persons infected in young adult life, pulmonary tuberculosis developed in 12.4 per cent.

Even if it is taken for granted that no difference has yet been shown between the significance of infection in these two age periods, that does not imply that it makes no difference to the individual patient whether primary infection takes place during childhood or during adult life. This problem can be looked at from other points of view. So far I have dealt mainly with the death rate from primary tuberculosis and early secondary forms of tuberculosis and with the incidence of phthisis, which is so frequent and therefore so hazardous, especially in young adult life. Even for those who do not acquire a fatal primary tuberculous infection or in whom a fatal secondary or tertiary form of tuberculosis does not develop,

14. Frölich, T.: Im Jahre 1912 vorgenommene Untersuchung über die Häufigkeit der tuberkulösen Infektion unter den Schulkindern Oslos. Nachuntersuchung im Jahre 1925, Acta pædiat. **7**:191, 1928.

15. Herlitz, G.: Studien über die Prognose der okkulten Kindertuberkulose, Acta pædiat. (supp. 2) **19**:1, 1937.

16. Myers, J. A.: Tuberculosis Among Children and Young Adults, Springfield, Ill., Charles C. Thomas, Publisher, 1938.

17. Wallgren, A.: Bidrag till tuberkulosens kliniska och experimentella patologi, Uppsala, E. Berling, 1918.

it is important whether infection takes place in childhood or in adult life. Consideration must also be paid to the morbidity rate and the significance the disease has for the infected person and his family in the two groups compared.

How frequently manifest tuberculosis develops in an adult who is in immediate association with a source of infection is not known for certain. As far as children, or at least infants, are concerned, it can be said that practically all of them manifest symptoms of infection. Only certain data relating to infection in young adult life are available: Of 507 primarily infected young adults, in 133, or 26 per cent, clinical disease developed. Thus from these figures one might conclude that primary infection produces symptoms of disease about four times as often in infants as in persons of young adult age.

Even if it were true that the first infection produces clinical primary tuberculosis more frequently in children than in adults, it is nevertheless more advantageous for the patient from a social, familial and economic point of view if the infection occurs during school age rather than in adult life. If a child of school age gets primary pulmonary tuberculosis and on that account has to be absent from school for some months, the economic loss to the family will not be more than the cost of medical attendance or hospital care. On the other hand, to an adult who has to earn his living and perhaps has a family to support, the loss of a few months' wages means much more. The health insurance movement, it is true, has done much to improve the family economy, but incapacity for work during illness nevertheless implies an economic loss to the nation, a factor which has no counterpart in the case of the child who is sick.

If these points of view are applicable to the question of generally transient, primary tuberculosis, they are still more valid with respect to that of the secondary type of tuberculous disease, serous pleurisy. Investigations carried out in Sweden [18] have proved that such pleurisy, with relatively few exceptions, appears within the first six or seven months after the manifestation of the primary tuberculosis. Whether it is more common after a primary infection in childhood than in later life is not known, but that is probably the case. It is well known, however, that serous pleurisy is also common in adults. In the statistics previously mentioned with regard to the incidence of primary infection in young adult life, I found records of 47 cases of pleurisy among 507 primarily infected adults, which is an incidence of 9 per cent. Arborelius gives the incidence as 33 per cent. In twenty-five per cent of the children who had had erythema nodosum in association with the manifestation of their primary tuberculous infection, pleurisy developed later.

18. Wallgren, A.: Pathogenesis of Acute Serofibrinous Pleurisy, Am. J. Dis. Child. **38**:829 (Oct.) 1929; footnote 6.

According to physicians who specialize in the treatment of tuberculosis, pleurisy demands a long period of care, as a rule six months or more. Judging from the persistent, increased sedimentation rate, such a long period of care cannot be regarded as excessive in the majority of cases. Unemployment of the head of a family for half a year may have a ruinous effect on the financial position of the family; and if it is the wife who is affected, it will be difficult for the husband to keep the home together without financial sacrifices. If a child is absent from school for the same length of time and his education cannot be continued during the illness, though that is possible in most cases, the worst that can happen is that he will have to remain in the same class for another year. A child's illness will not have so serious an effect on the family's financial position as the sickness of an adult member would have.

A third, fortunately less common, disease which may have a still more serious influence in the same respects as have been mentioned is tuberculosis of the bones and joints. The onset of this condition, too, seems to show a certain time relation to the manifestation of active primary tuberculosis. The results of certain investigations [19] indicate that tuberculosis of the bones and joints appears within the first three years after a primary infection, especially within the first two years. It is not known whether the frequency of this disease is higher in childhood than in adult life. In all events, the number of adult patients with bone and joint tuberculosis is great, as witnessed by the number of patients in seaside hospitals. If the localization is unfavorable and the process malignant, an attack of this disease may mean invalidism for many years, with unfortunate consequences for the patient and his family. During the period of care a child can receive educational instruction, and after the disease is cured if he is permanently disabled he can be taught a suitable trade at one of the hospitals for the crippled which will enable him to earn a living. For an adult to learn a new trade suited to the nature and degree of his disability means a great loss of valuable time, with financial and social consequences for his family and for the community.

I should like to summarize what has been said as follows: Experience shows that under all circumstances infection during the first years of life is a disadvantage because of the hazard of death from primary tuberculosis and of the development of early secondary tuberculous diseases in this period of life. The risk is less in all other age periods. If attention is paid exclusively to the malignancy of primary tuberculosis, it appears immaterial whether infection takes place during the school age before puberty or in young adult life. Since manifest tuberculosis after

19. Wallgren, A., and Lundblom, A.: Ueber den Zeitpunkt des Auftretens der Skelettuberkulose, Tuberkulose **15**:164, 1935.

a primary infection occurs more frequently when infection is acquired in childhood than when it takes place in adult life, infection in childhood from a purely medical point of view is a greater disadvantage. However, manifest primary tuberculosis is so common among young adults too that primary infection at that age must be regarded from a social point of view as a greater advantage because of the amount of care required and the consequences of the disease. This is true to a still greater extent of serous pleurisy, which is about as frequent after a primary infection in adult life as in childhood and which is of great social importance when it occurs in adults because of the long period of care required. The risk of the occurrence of tertiary pulmonary tuberculosis (phthisis) has not been shown to be greater when infection is acquired in childhood than when it occurs in young adult life, and in that respect there is no reason to believe that childhood infection is more disadvantageous. On the basis of theory, supported by practical experience, one can say, on the contrary, that pulmonary tuberculosis probably develops more readily from a fresh, active primary complex in the lung acquired during the age of predilection of phthisis than from an old, healed and immunizing childhood infection.

If the advantages and disadvantages of postponing the primary tuberculous infection until young adult life are weighed against each other in this way one can hardly conclude, without making some reservations, that it is advantageous for a child to pass through school age without being infected. Instead, in my opinion, it is an advantage for a person to enter the critical period of young adult life with a well healed childhood infection behind him.

If these conclusions are true, and in my opinion one can hardly doubt their validity, the results of prophylaxis against tuberculosis so far appear in a somewhat odd light. Prophylactic work has resulted in the postponement of tuberculous infection in an increasing number of cases until adult life, and after a few more generations a child will acquire infection only in exceptional cases. It is true, then, that tuberculosis prophylaxis is on the wrong path and that one should try to obtain a return to the conditions of earlier times, when childhood infection predominated? I believe that no change in that direction will ever take place and that without a doubt efforts must be continued to postpone infection as long as possible, with the hope that it will never occur. To prevent infection altogether is of course the main and the only rational object of the prophylaxis of tuberculosis.

However, since some prophylactic measures may possibly expose noninfected and nonimmunized young persons to a certain increased risk, efforts should be made to utilize all the means available to diminish this risk. As far as can be judged, such a means is available in BCG vac-

cination. The experiences of many workers who are using this vaccination in a rational manner [20] speak so unanimously in its favor that it cannot be ignored. Their experiences sustain the statement of Calmette that BCG vaccination confers a specific protection of the same kind, if not of the same degree, as the immunity produced by a primary infection, without subjecting the vaccinated person to any risks. By vaccinating with BCG those persons who pass through childhood without infection the possible disadvantages involved in postponing the primary infection until young adult life may be neutralized, at least to some extent.

The conclusion I wish to draw from the points of view and experiences discussed here is that efforts to postpone tuberculous infection indefinitely are worth while and rational, but they should be supplemented by BCG vaccination of noninfected school children at the age of puberty.

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20. Heimbeck, J.: Immunity to Tuberculosis: Relation of Cutaneous Allergy and Resistance to Tuberculous Infection Following Vaccination with BCG, Arch. Int. Med. **49**:957 (June) 1932. Kerezturi, C.; Park, W. H., and Logie, A. J.: A Study of 2900 Chest Roentgenograms of BCG-Vaccinated and Control Infants in Tuberculous Families, Nat. Tuberc. A., Tr. **31**:97, 1935. Wallgren, A.: Value of Calmette Vaccination in Prevention of Tuberculosis in Children, J. A. M. A. **103**:1341 (Nov. 3) 1934. Anderson, H., and Belfrage, H.: Ten Years' Experience of BCG-Vaccination at Gothenburg, Acta pædiat. **26**:1, 1939.

OSTEITIS FIBROSA CYSTICA (ALBRIGHT)

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In April 1937 Albright and his co-workers in Boston reported 5 cases in which were presented the bizarre concurrent features of osteitis fibrosa cystica, areas of pigmentation of the skin and endocrine dysfunction, with premature puberty in the female patients. Although 12 similar cases had previously been reported in the literature under a variety of titles, beginning with Weil's report in 1922, the paper of Albright and his associates was the first to establish this peculiar syndrome as a clinical entity distinctly separate from, rather than an aberrant type of, one of the other known diseases affecting bone. For this reason and because there is no simple term to encompass all the prerequisite elements, in the "Standard Classified Nomenclature of Disease" the term "Osteitis Fibrosa Cystica (Albright)" has been adopted to identify this particular disease picture.

CHARACTER OF THE SYNDROME

The osseous disorder in this group of cases is one of osteitis fibrosa cystica, unassociated with any consistent laboratory evidence of disturbance in the metabolism either of calcium or of phosphorus. The only laboratory finding of note in relation to the osseous disease is the frequently observed increase in the blood phosphatase. This elevation probably reflects the augmented osteoblastic activity (bone repair) resultant from the abnormally great stress and strain imposed on the bones by intrinsic osseous disease. Therefore, as might be expected, the values for phosphatase are roughly proportional to the extent of involvement of the skeleton. The distribution of the lesions has, in the majority of instances, tended to be more or less lateralized. Exceptions to this have been noted in cases in which males were affected or cases in which the skull was involved. The distribution of the lesions, moreover, is spotty, some bones being markedly diseased while their neighbors appear untouched. The carpal bones and the epiphyses are usually little, if at

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all, affected (fig. 5). The skull, when involved, shows cystic degeneration of the calvarium and a hyperostotic sclerosing process in the base (fig. 2). The latter process may progress to complete obliteration of the mastoid cells and the accessory nasal sinuses. Generalized decalcification of the bones is unusual. Scattered areas of increased density, either linear or irregular in configuration, are intermingled with areas of rarefaction simulating cysts. The involved bones may be markedly expanded (fig. 4). Bone age is increased in females and usually unaffected in males. Biopsy, with few exceptions,[1] has shown the presence of typical fibrosing osteitis, with a notable lack of osteoclasts (fig. 8).

The pigmentation seen in these cases consists of flat, patchy, light brown areas, which tend to occur on the buttocks, the sacral and the lumbar regions and the back of the neck (fig. 1). Biopsies have shown that the areas are due to localized accumulations of melanin in the skin. The pigmentation resembles that seen in cases of neurofibromatosis.[2] It has been stated that the amount of pigmentation is roughly proportional to the severity of osseous disease; the pigmented areas also tend to be ipsilateral to the osseous lesions when the latter are predominantly one sided and bilateral when they are widespread.

The third element, endocrine dysfunction, seems almost to be limited to females. Precocious puberty, with onset of menstruation at an average age of approximately 3 years, occurred in nearly 70 per cent of the total number of cases reported in which the disease affected females. In addition, advanced bone age was found in practically all cases of the disease in females in which this feature was specifically evaluated. On the other hand, in only 2 cases did any signs appear in males which could be interpreted as possible evidence of early sexual development. In both of these (Albright's cases 5 and 7) there were signs of approaching puberty at the borderline age of 12 years, and in both a somewhat advanced bone age was exhibited. Four instances [3] of hyperthyroidism were reported, in 3 of which the patients were females. The differences between the manifestations of the syndrome in males and in females are striking, therefore, and constitute one of the most interesting features of the syndrome.

REVIEW OF THE LITERATURE

As far as can be ascertained, 23 cases in which all of the characteristics described by Albright were present have been recorded in the literature from 1922 through 1939. Data in these cases are presented

1. Hummel; Snapper and Parisel.
2. McCune; McCune and Bruch; Stalmann.
3. McCune; McCune and Bruch; Summerfeldt and Brown; Barnwell.

in table 1, which is self explanatory. Many of these cases, as can be noted, have additional elements of interest, there being a particularly high incidence of severe jaundice or gastrointestinal disturbances in the

TABLE 1.—*Data in Twenty-Three Cases Reported in the Literature in Which*

Author	Date	Sex of Patient	Age of Patient, Yr.	Roentgenologic Diagnosis	Diagnosis from Biopsy	Bone Age	Precocious Puberty	Areas of Pigmentation	Level of Blood Calcium	Level of Blood Phosphorus
Weil	1922	♀	9	O.F.C.	.....	Advanced	+ at 1 yr.	+	.....	.....
Hirsch	1929	♂	30	O.F.C.	O.F.C.	.....	0	+	N	.....
Priesel and Wagner	1932	♂	13	O.F.C.	.....	.....	0	+	N	.....
Freedman §	1932	♂	6¾	O.F.C.	.....	.....	0	+	Slightly >	Slightly >
Gaupp	1932	♀	9	O.F.C.	O.F.C.	Advanced	+ at 9 yr.	+	N	N
Stalmann	1933	♀	8	O.F.C.	.....	.....	+ at 9 mo.	+	N	N
Snapper and Parisel	1933	♀	10	O.F.C.	†	.....	+ at 7 yr.	+	.....	.....
Goldhamer	1934	♀	9	O.F.C.	O.F.C.	.....	+ at 2 yr.	+	N	N
Hummel	1934	♂	11	? O.F.C.	‡	.....	0	+	.....	.....
		♂	9½	? O.F.C.	‡	.....	0	+	.....	.....
McCune	1936	♀	9	O.F.C.	O.F.C.	Advanced	+ at 2 yr.	+	N	N
Albright, Butler, Hampton and Smith	1937	♀	23	O.F.C.	O.F.C.	Advanced	+ at 7 yr.	+	N	N
		♀	39	O.F.C.	O.F.C.	Advanced	+ at 1 yr.	+	Slightly <	Slightly <
		♀	3½	O.F.C.	O.F.C.	Advanced	+ at 4½ mo.	+	N	N
		♀	8	O.F.C.	O.F.C.	.....	+ at 3½ yr.	+	N	N
		♂	10	O.F.C.	O.F.C.	? Slightly advanced	? at 12 yr.	+	N	N
Albright, Scoville and Sulkowitch	1938	♂	21	O.F.C.	.....	.....	0	+	> (1 determination) N (1 determination)	> (1 determination) N (1 determination)
		♂	14	O.F.C.	O.F.C.	Slightly advanced	? at 12 yr.	+	N	N
Barnwell	1938	♂	11	O.F.C.	.....	.....	0	+	Variable levels	
Braid	1939	♂	11	O.F.C.	.....	.....	0	+	N	N
		♀	3	O.F.C.	.....	.....	+	+	N	N
Summerfeldt and Brown	1939	♀	3	O.F.C.	O.F.C.	.....	+ at 3 yr.	+	.....	.....
		♀	2	O.F.C.	O.F.C.	.....	+ at 2 yr.	+	.....	.....

* O.F.C. means osteitis fibrosa cystica; the symbol + signifies present; N, normal; F.S.F., follicle-stimulating factor; E.S., estrogenic substance; >, increased and <, decreased.

neonatal period and of hyperthyroidism. It is also interesting to note the variety of descriptive terms employed. Hummel called his 2 cases instances of "juvenile Paget's disease," on the basis of biopsies, which

showed the mosaic structure typical of that condition, but according to Albright the published photomicrographs are not convincing. Freedman reported his case as an example of probable adrenal dysfunction.

the Characteristics of the Syndrome Described by Albright Were Present *

Level of Blood Phosphatase	Excretion of Calcium	Level of Blood Cholesterol	Dextrose Tolerance Curve	Basal Metabolic Rate	Excretion of Gonadotropic and Estrogenic Substances	Severe Neonatal Jaundice	Condition of Parathyroids at Operation	Comment
..	.....	.....	.....	..	.....	..	.....	
..	.....	.....	.....	..	.....	..	Normal	One normal parathyroid removed, without benefit
..	.....	.....	.....	..	.....	..	Normal	One normal parathyroid removed, without benefit
..	.....	.....	.....	..	.....	..	.....	Tendency to severe bleeding; platelets normal
..	N	.....	.....	..	.....	..	Normal	
..	.....	.....	.....	..	.....	..	.....	"Neurofibromatosis"
..	.....	N (3 determinations) > (1 determination)	.....	N	.....	..	Normal	Mental deficiency
..	.....	N	.....	..	.....	..	.....	Epulis
..	.....	.....	.....	..	.....	..	.....	
..	.....	.....	.....	..	.....	..	.....	
>	N	N	Flat	>	F.S.F. > E.S. >	+	Normal	"Atypical neurofibromatosis"
N	N	N	.....	..	F.S.F. N	..	.....	
N	N	N	.....	..	F.S.F. N E.S. >	..	.....	
>	N	N	N	..	F.S.F. N E.S. N	..	.....	Reported previously by Freedman, as case of "adrenal dysfunction;" fatty diarrhea in infancy; mental deficiency; adrenals normal at operation; simple ovarian cyst; autopsy performed
N	.....	N	.....	..	.....	..	.....	
>	N	N	Flat	..	F.S.F. N	..	Normal (2 operations)	Two normal parathyroids removed; transient tetany
>	Negative balance	N	Slightly high	..	F.S.F. N	..	Normal	Positive neurologic findings; I. Q. of 90; emotional instability; bilateral gynecomastia
>	N	N	.....	N	.....	..	Normal	
..	.....	<	.....	>	.....	..	Normal	Died after thyroidectomy; autopsy performed
>	N	.....	.....	..	.....	+	.....	"Osteodystrophy following icterus gravis"
>	N	.....	.....	..	.....	+	.....	"Osteodystrophy following icterus gravis"
>	Slightly negative balance	>	.....	>	.....	..	Normal	"Osteodystrophia fibrosa"
..	.....	>	Flat	>	.....	+	.....	"Osteodystrophia fibrosa"

† "Xanthomatosis."
‡ "Juvenile Paget's disease" (photomicrographs not convincing).
§ See case 3 of Albright, Butler, Hampton and Smith.

Snapper and Parisel reported their case as an instance of xanthomatosis (because one of four determinations showed that the level of cholesterol in the blood was elevated and one of three biopsies disclosed cholesterol

crystals and "foam cells"). Braid dubbed the condition in his 2 cases "osseous dystrophy following icterus gravis," because both of his patients had severe jaundice soon after birth. Summerfeldt and Brown labeled the disease in their cases "osteodystrophia fibrosa." McCune, McCune and Bruch and Stalmann expressed the belief that their cases were examples of atypical neurofibromatosis.

In addition to these 23 cases, there are at least 10 others on record which in all probability belong to this syndrome but in which one or more of its characteristic elements were lacking. Data in these cases are presented in table 2. For example, the areas of pigmentation were missing in Gaupp's and in Salzer's cases; precocious puberty was not present in the case of Gorham, Campbell and Howard, and precocious puberty and areas of pigmentation were both absent in the cases of Lichtenstein, Freund and Freund and Meffert. Occurrence of the syndrome in its complete form is undoubtedly rare; however, occurrence in its incomplete forms must be fairly common. It seems unreasonable to assume that the syndrome occurs exclusively in any set form until it is further understood.

Necropsies have been performed in 2 cases (Freedman, Barnwell). In neither was the central nervous system explored. Freedman's report of his observations at autopsy is not yet available. The death of Barnwell's patient followed thyroidectomy, and autopsy showed a "diffuse colloid goiter" and an enlarged thymus. No parathyroid adenoma or other unusual pathologic changes were found.

To the 23 cases of the complete form of the syndrome, for which data are listed in table 1, the following case, that of a patient in the children's ward of the Wisconsin General Hospital, is to be added. The nature of the disease was suspected clinically and was substantiated by special tests; that the case should be classed as an example of the syndrome was verified by Dr. Fuller Albright,[4] of Boston.

REPORT OF A CASE

R. S., a boy aged 7 years and 2 months, entered the Wisconsin General Hospital for the first time on Nov. 8, 1939; he had been referred by his family physician for the diagnosis and treatment of a defect of his skull.

History.—The boy, the fourth of five children, was born at full term on Sept. 10, 1932. All siblings are alive and well. There was no history of familial disease. The weight at birth was 5¾ pounds (2,608 Gm.). There were no immediate neonatal disturbances, but at the age of 2 weeks the child began to have "digestive upsets" and to vomit the greater part of his formula. His appetite failed, and his weight stopped increasing and soon began to decline. This condition continued until the age of 3 months, at which time the child weighed approximately 3 pounds

4. Personal communication to the author.

TABLE 2.—*Data in Ten Cases Reported in the Literature in Which Some Characteristics of the Albright Syndrome Were Present* *

Author	Date	Sex of Patient	Age of Patient, Yr.	Roentgenologic Diagnosis	Diagnosis from Biopsy	Bone Age	Precocious Puberty	Area of Pigmentation	Level of Blood Calcium	Level of Blood Phosphorus	Level of Blood Phosphatase	Excretion of Calcium	Condition of Parathyroids at Operation	Comment
Salzer	1930	♀	..	O.F.C.	.....	.....	+							
Gaupp	1932	♀	8	O.F.C.	O.F.C.	Advanced	+ at 3 yr.	..	N	..	.....	..	Normal	
Freund	1934	♀	12	O.F.C.	O.F.C.	.....	.....	..	N	..	.....	..	Normal	Roentgen therapy to parathyroids, with no benefit
		♀	13	O.F.C.	O.F.C.	.....	.....	..	N					
		♀	23	O.F.C.	O.F.C.	.....	.....	..	N					
Gorham, Campbell and Howard	1937	♀	..	O.F.C.	.....	.....	?	+						
Lichtenstein	1938	♀	..	†	‡	.....	0	..	N	N	Slightly >	N		
		♀	..	†	‡	.....	0	..	N	N	Slightly >	N		
		♀	..	†	‡	.....	0	..	N	N	.....	N		
		♂	..	†	‡	.....	0	..	N	N	.....	N		

* O.F.C. means osteitis fibrosa cystica; the symbol + signifies present; N, normal; >, increased.
† "Polyostotic fibrous dysplasia."
‡ "Fibrosing osteitis."

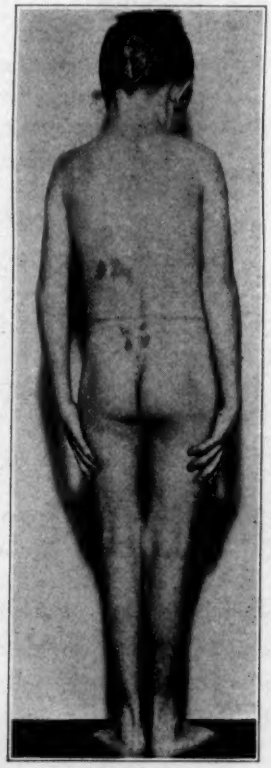

Fig. 1.—Photograph of the patient, showing areas of pigmentation and healed surgical scar on the occiput.

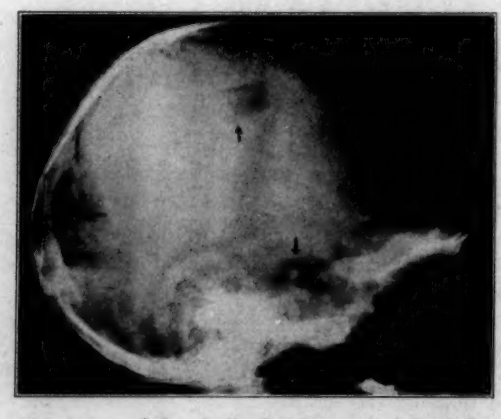

Fig. 2.—Roentgenogram of the skull, showing well defined "cystic" areas in the calvarium and sclerosis of the base.

Fig. 3.—Roentgenograms of the humeri, showing expansion of the proximal third of the right humerus.

Fig. 4.—Roentgenogram of the pelvis, showing disseminated fibrocystic lesions.

(1,307 Gm.) and was described by his aunt as looking "all dried up," with loose skin, shrunken face and pipestem-like arms and legs. The skin was at first described as "jaundiced," but closer questioning elicited the statement that it was "a peculiar bluish color." The child was hospitalized at this time, and injections of physiologic solution of sodium chloride and dextrose in addition to careful building up of the diet arrested the condition within a month's time. On discharge, the child was taking a diet of lactic acid whole milk, dextrimaltose and water, interspersed with feedings of orange juice and cod liver oil in adequate amounts. This diet was well tolerated. He soon regained the lost ground and became a healthy, normal child. He sat up by himself at 8 months and walked at 14

Fig. 5.—Roentgenograms of the hands and arms, showing normal carpal bones and epiphyses, comparatively normal ulnas and radiuses and markedly diseased bones of the hands.

months of age and cut his deciduous teeth promptly. At the age of 1½ years pigmented spots on his back were first noted. These areas are said to have remained the same in size since discovery. At 4 years of age the boy had measles, without complications, and soon after contracted whooping cough, which ran an uneventful course. When he was 4½ years old, he fell from a slide and fractured his left arm above the elbow. Roentgenograms were taken, the fracture was set and healing followed in the usual time. However, just after the arm had healed, the patient fell out of a chair and refractured the bone in the same place. Again roentgenograms were taken, the arm was set in a cast and healing followed

promptly. Nothing unusual about the bones was noted in either roentgen examination. At 6 years of age, the boy fell from a wagon and fractured his left femur; skeletal traction by means of a Kirschner wire through the os calcis was required for healing. The roentgenograms taken at that time have been examined and give evidence of the presence of generalized slight osteoporosis, with no definite cysts anywhere. They were considered normal by the local physician who diagnosed and treated the fracture. From the time this last fracture healed until the beginning of the present illness, the boy appeared perfectly normal. He was mentally alert and physically active.

Present Illness.—The present illness began the latter part of October 1939, when the father, while cutting the boy's hair, discovered a slightly protuberant, somewhat tender, egg-sized mass on the back of the head. A physician was consulted; his diagnosis and treatment are best presented by the following condensed excerpt from his letter:

Fig. 6.—Roentgenograms of the feet, showing marked disease of the bones.

"The history of rapid onset and the appearance and tenderness of the lesion led me to believe that the mass was an infected cyst. With the use of local anesthesia, induced by procaine hydrochloride, I incised the skin over the lesion; when I found, however, that under pressure with blunt forceps the mass slipped away, I decided that it was either a multilocular cyst or a fatty tumor, which would have to be removed in a hospital. At the hospital, dissection of the tumor went well for a while, but eventually the wall of the mass ruptured and I found that the lesion was a meningocele, or at least a protrusion of the meninges through an opening in the skull. I closed the wound and sutured the scalp, and the next day I had a stereoroentgenogram of the skull made. I discovered that the skull had not only the defect discovered at operation, which measured 1½ inches

(3.8 cm.), but other large ones and several small ones, in widely scattered locations. Herniation of the coverings of the brain had not occurred through any other of the osseous defects."

Physical Examination.—Examination on admission revealed a well developed, well nourished boy in no distress. The skin was normal except for two flat, irregular brown spots over the left costovertebral region and several more overlying the upper part of the sacrum, just to the left and the right of the midline (fig. 1). The majority of the areas of pigmentation were on the left side. Examination of the head revealed a healed vertical operative scar over the occipital region (fig. 1). A definite bony defect, measuring approximately 1½ by 2 inches (3.8 by 5 cm.), could be palpated in the skull underlying the scar (fig. 2) There was

Fig. 7.—Roentgenograms of the tibias and femurs, showing (1) site from which the specimen was removed for biopsy and (2) site of the old fracture.

a flattening defect in the right posterior parietal region. The frontotemporal ridges were prominent, as were the mastoid processes. The supraorbital ridges, the frontal bosses and the mandible were underdeveloped. The mouth and the pharynx were normal except for hypoplastic and carious deciduous teeth. There were no masses in the neck, and the thyroid was not palpable. The chest was of normal size and shape. The lungs were normal to all modes of examination. The cardiac examination gave normal results. The blood pressure was 118 mm. of mercury systolic and 60 mm. diastolic. Examination of the abdomen showed no pathologic condition. The right shoulder appeared larger than the left because of enlargement of the proximal third of the humerus (fig. 3). There was marked lateral bowing of the femurs. The legs were disproportionately thin, and the tibias felt

smaller than normal. The child was slightly below average height for his age. Neurologic examination gave negative results.

Laboratory Data.—The number of the cellular elements of the blood was within the normal range. The level of serum calcium ranged from 9.2 to 10.5 mg. per hundred cubic centimeters and that of inorganic phosphorus from 3.4 to 3.6 mg. Determinations of phosphatase on two occasions, with an interval between the examinations, showed elevation to 13.4 and 17.8 Bodansky units per hundred cubic centimeters of serum. Values for serum protein were 5.2 and 5.6 Gm. per hundred cubic centimeters. Values for blood cholesterol on two occasions proved to be well

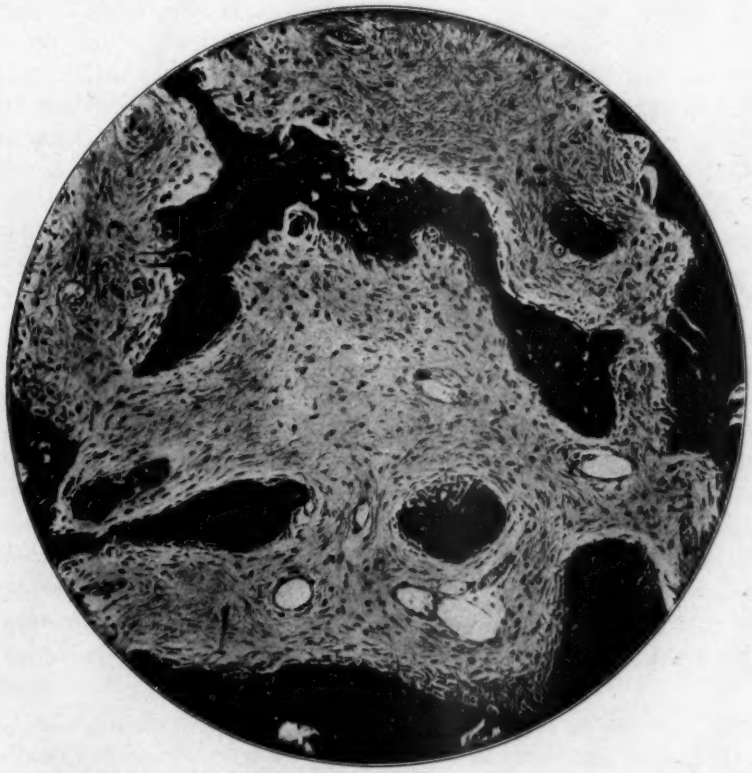

Fig. 8.—Section of bone removed for biopsy. Note the scarcity of osteoclasts. Low magnification.

within the normal range. The levels of sugar and nonprotein nitrogen in the blood were normal. A dextrose tolerance test showed a fasting level of 115 mg. of sugar per hundred cubic centimeters of blood, which rose to 230 mg. in thirty minutes, fell to 163 mg. in sixty minutes, to 110 mg. in one hundred and twenty minutes and to 84 mg. in one hundred and eighty minutes. Examinations of the urine gave repeatedly normal results. There was no Bence Jones protein in the urine. Two seventy-two hour quantitative calcium excretion tests, done while the patient was on a measured low calcium diet, each showed a slightly positive calcium balance. Determinations of the content of gonadotropic (follicle-stimulating) substance of 3 twelve hour specimens of urine gave normal results.

Roentgen Examination.—Roentgenograms of the skeleton showed widespread decalcification and areas of cystic rarefaction, which were most definite in the skull (fig. 2), the iliums, the proximal portion of the femurs (fig. 4), the hands (fig. 5), the feet (fig. 6), the scapulas and the tibias (fig. 7). The bones which did not show well defined cystic areas had a coarse reticular structure. The bone age was normal (fig. 5). There was marked hyperostosis of the base of the skull (fig. 2).

Esophagograms, taken in an attempt to locate pressure defects caused by a possible enlargement of the parathyroids, were reported to be normal.

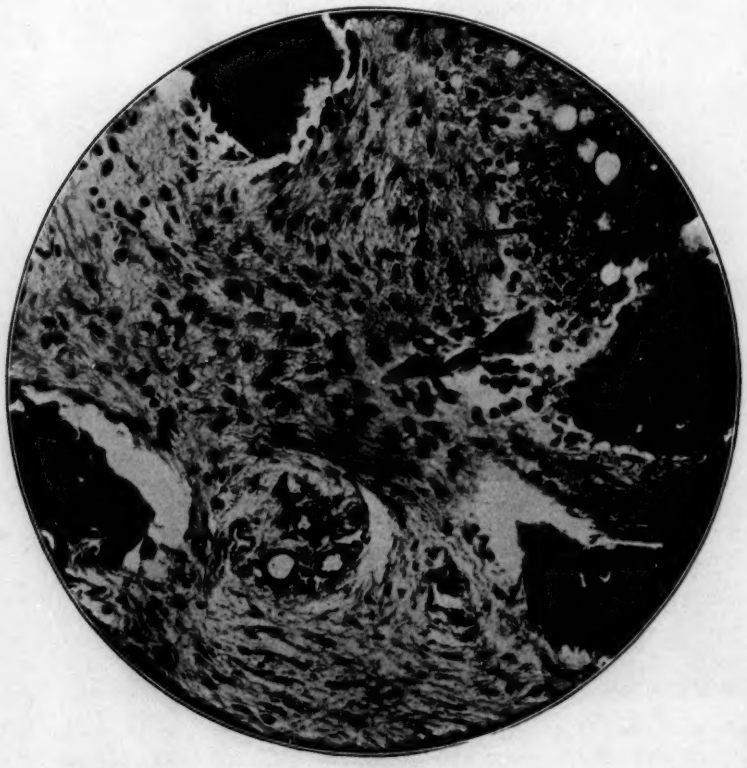

Fig. 9.—Section of bone removed for biopsy. Note the area of hemorrhage. High magnification.

Biopsy.—On Dec. 16, 1939 a specimen of bone for biopsy was taken from the right tibia (fig. 7). Superficially, the bone appeared normal. The cortex was of normal density but not of uniform thickness. On removing a window of cortex, areas of dense fibrosis were found in the marrow. Microscopic examination revealed areas of normal marrow merging into other areas of dense fibrosis containing many fine trabeculae of bone (fig. 8). There were, in addition, several small hemorrhages surrounded by young fibroblasts, which became more and more mature as one progressed peripherally (fig. 9). Some inflammatory cells were present (fig. 9). Osteoblastic activity was predominant over osteoclastic activity; that is, bone repair exceeded bone destruction (fig. 8). The section was reported typical for a case of fibrosing osteitis.

COMMENT

Many of the widely different theories as to the cause of this odd syndrome can be excluded. Active hyperparathyroidism seems to be ruled out by the spotty distribution of the lesions, the consistently normal results of studies of calcium and phosphorus metabolism and the repeatedly fruitless exploratory operations on the neck. If anything, the lesions microscopically resemble the picture seen in cases of healing or healed hyperparathyroidism (Bauer). That Paget's disease is the cause is improbable because of the average age at onset in cases of this condition, the nonpathognomonic results of biopsies and the related elements of the syndrome. Ollier's disease is ruled out because the lesions are not confined to cartilage bone. The presence of xanthomatosis is questionable because in the vast majority of cases there is no evidence of it in the results either of biopsies or of studies on the blood. Multiple myeloma is ruled out by the benign course, the age level and the results of biopsy. Atypical neurofibromatosis as a diagnosis has little to support it except the similar appearance of the areas of pigmentation in the two diseases. Adrenal dysfunction is doubtful. Albright's case 3 was previously reported by Freedman as an example of adrenal dysfunction, but an exploratory operation done later revealed no pathologic condition in either adrenal gland. A primary ovarian disturbance has never been proved, the most ever found on exploration of the ovaries having been small simple cysts (Freedman). The distribution of the lesions militates against a metabolic disorder. The usual causes of precocious puberty, namely, disturbances which are primarily ovarian, testicular, pituitary, pineal, adrenal or thymic, seem either to be ruled out or to be highly improbable. What, then, can be said about the cause of the condition? In answering this question, it must be stated that one is forced, in the absence of more conclusive data, to deal only with theoretic considerations.

Albright suggested that all the elements might be due to a primary widespread neurologic defect, probably on an embryonic basis. He preferred this neurogenic theory, because by it he could explain hypothetically, on the assumption of a hypothalamic defect, the endocrine dysfunction, including the discrepancy between the manifestations in males and in females. His theory is well worth considering; it is expressed in his original article. Evidences to support this theory are: the occurrence of similar areas of pigmentation in cases of neurofibromatosis, the occurrence of mental deficiency in several cases, the marked emotional instability observed in others, the presence of peripheral signs of a neurologic disorder in 1 case and the fact that gliomas or pinealomas involving or exerting pressure on the hypothalamic region have been known to cause precocious puberty.

It seems improbable, despite Albright's heroic and ingenious attempts, that any single factor can be made to account for all the elements of the syndrome. It appears more logical to assume the presence of embryonic defects affecting multiple systems rather than a single one. The fact that the elements probably occur individually in patients much more frequently than they occur simultaneously seems evidence against a defect in a single system. The areas of pigmentation are certainly of common occurrence. Bone cysts and disseminated fibrocystic disease of this type can occur without areas of pigmentation, precocious puberty or hyperparathyroidism.[5] This may represent merely misdirected metamorphosis of the mesenchymal stem cells of bone, which ordinarily give orderly origin to bone cells, fibroblasts, osteoclasts and cartilage (Lichtenstein). The occurrence of islands of cartilage in several cases and the osteoclastoma in Goldhamer's case are explainable by this assumption. The endocrine dysfunction probably is, as Albright suggested, best explained by a hypothalamic defect. Thus multiple systems seem to be affected, and at least two germ layers are involved. It must be stated that any theory which accepts embryonic defects as a causative mechanism constitutes a therapeutic stymie and therefore should not be accepted until other etiologic agents more amenable to control have been excluded. Further study and experimentation are certainly in order before any dogmatic conclusions can be drawn. The first autopsy which includes an examination of the central nervous system will be of great interest.

SUMMARY

The case of a young boy is presented in which there was a history of marasmus in infancy, pigmented spots and frequent fractures. Roentgen evidence of fibrocystic disease was supported by the results of biopsy, and the blood and the urine were normal to both chemical and microscopic analysis except for an increase in the level of blood phosphatase. This case is shown to belong to a syndrome described by Albright in 1937. A brief description of the syndrome, a review of the pertinent literature and a discussion of certain theoretic considerations are presented. Multiple embryonic defects seem the most likely causative mechanism.

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Abstracts from Current Literature

Biochemistry; Bacteriology, and Pathology

IN VITRO EFFECT OF PECTIN AND NICKEL PECTIN ON BACTERIAL GROWTH. P. S. PRICKETT and N. J. MILLER, J. Pediat. **15**:710 (Nov.) 1939.

Among the hypotheses proposed to explain the favorable action of pectin in diarrhea is one that pectin exerts a bactericidal effect. Thirteen different commercial pectins were tested to determine the effect on the growth of Escherichia coli. No effect on the growth could be attributed to the pectin per se. Whatever unfavorable effect was noted in pectin broth was found to be a result of the effect of pectin on the acidity of this broth. The effect of nickel in various concentrations on the growth of Esch. coli was studied in the absence and in the presence of pectin. The bactericidal effect of nickel varied directly with its concentration.

RAUH, Cincinnati.

Metabolism; Infant Feeding; Milk and Other Foods

THE RATE OF OCCURRENCE OF HYPOGLYCEMIA. JAMES FINLAY HART and JAMES R. LISA, Endocrinology **27**:19 (July) 1940.

In the course of determining 21,000 routine values for "fasting blood sugar," values below 80 mg. per hundred cubic centimeters were found to be common and values below 70 mg. not unusual. Values as low as 28 mg. were found without shock.

The authors conclude that either spontaneous hypoglycemia is not a common condition or routine determinations of "fasting blood sugars" are not reliable guides to its occurrence.

JACOBSEN, Buffalo.

THE METABOLISM OF CITRIC ACID BY INFANTS. ARTHUR H. SMITH and D. J. BARNES, J. Nutrition **20**:255 (Sept.) 1940.

The subjects of this balance study were 8 infants 4 to 12 months of age, who had mild clinical rickets but were otherwise normal. This study dealt with the comparison of the metabolism of free citric acid and of food citrate as determined by the balance method. The authors present data which show that free citric acid given orally resulted in a definite decrease in the proportion of the ingested citric acid and citrate from food which appeared in the urine, as compared with the control period in which the only source of citric acid was the food citrate of the basal diet. The citric acid of the feces was not influenced by the addition of free citric acid.

FREDEEN, Kansas City, Mo.

THE UTILIZATION OF THE CALCIUM OF DI-CALCIUM PHOSPHATE BY CHILDREN. ELIZABETH KEMPSTER, HERTA BRIETER, ROSALIND MILLS, BEULA MCKEY, MARIE BERNDS and JULIA OUTHOUSE, J. Nutrition **20**:279 (Sept.) 1940.

Kempster and her associates, using 6 preschool boys for their metabolic studies, fed two levels of calcium, 350 mg. and 500 mg. daily, both of which were below the minimal requirement for maximal retention but in excess of possible maintenance requirement. The difference of the two levels was due mainly to the supplementation of the basal diet with 543 mg. of dicalcium phosphate daily. The utilization of the calcium averaged 19.5 per cent, and with milk these same children in a previous study utilized 19.8 per cent of the calcium, which showed that the dicalcium phosphate source of calcium was not superior to that of milk.

FREDEEN, Kansas City, Mo.

PECTIN ENZYMES: V. THE FATE OF PECTINS IN THE ANIMAL BODY. Z. I. KERTESZ, J. Nutrition **20**:289 (Sept.) 1940.

Kertesz, using human subjects and dogs, obtained data showing that pectin taken orally is apparently not acted on until it reaches the large intestine, where it is completely hydrolyzed by bacterial enzymes. In vitro pectin incubated with feces was rapidly decomposed, but with trypsin, pepsin and rennet there was no effect.

FREDEEN, Kansas City, Mo.

NITROGEN METABOLISM DURING THE ORAL AND PARENTERAL ADMINISTRATION OF THE AMINO ACIDS OF HYDROLYZED CASEIN. A. T. SHOHL, A. M. BUTLER, K. D. BLACKFAN and E. MACLACHLAN, J. Pediat. **15**:469 (Oct.) 1939.

The purpose of the present study was to test whether the amino acids supplied by casein were adequate for nutrition so far as could be determined by measurements of nitrogen balance over short periods. These studies were carried out on infants during oral and intravenous administration of an enzymatic hydrolyzate of casein. The product used contained 11.9 per cent nitrogen, of which over 60 per cent was present as amino acids; no protein was present. The results showed that the amino acids administered orally in the presence of the non-nitrogenous dietary essentials gave positive nitrogen balances in all cases. Positive and sufficient nitrogen balances were obtained by the intravenous administration of hydrolyzed casein together with dextrose and sodium chloride. In most instances, the intravenous administration of the amino acids caused reactions, most prominently a marked elevation of temperature.

RAUH, Cincinnati.

THE USE OF IRRADIATED EVAPORATED MILK IN INFANT FEEDING. R. W. B. ELLIS, Arch. Dis. Childhood **14**:295 (Dec.) 1939.

Twenty normal full term infants were given irradiated evaporated milk as their sole source of orally taken vitamin D during three to six months between October and April. At the end of three months 1 infant showed roentgen evidence of mild active rickets, and 2, of healed rickets. Seven infants suffering from active rickets were treated as inpatients, with irradiated evaporated milk as their sole source of vitamin D. In all cases, evidence of healing was seen in from one to three weeks. It is concluded that although the brand of irradiated evaporated milk used will serve to protect the majority of full term infants from manifest rickets, it cannot be relied on to protect all. That the milk in question has considerable antirachitic properties is shown by the response of the rachitic group. It should therefore serve as a valuable source of vitamin D, particularly for infants who receive vitamin D supplement irregularly or in insufficient amounts. The milk should not, however, be relied on as the sole source of vitamin D, particularly in the case of prematurity. The milk was found easy to use, and was taken well by the great majority of infants. No ill effects were observed from prolonged administration of the milk.

KELLY, Milwaukee.

Vitamins; Avitaminoses

VITAMIN D POTENCY OF HUMAN BREAST MILK. R. S. HARRIS and J. W. M. BUNKER, Am. J. Pub. Health **29**:744 (July) 1939.

Harris and Bunker assayed 15 gallons (57 liters) of winter human milk by feeding the nonsaponifiable fraction of the milk fat to rats. The milk assayed only 4 U.S.P. XI units of vitamin D per quart. The authors conclude that the superiority of human milk in preventing and curing rickets in infants cannot be attributed entirely to its vitamin D content. Comparing the present assay with previous assays, they conclude that the antirachitic potency of human milk can be increased fivefold by feeding metabolized milk to the lactating mother.

LIMPER, Louisville, Ky.

THE VITAMIN C REQUIREMENT OF MAN ESTIMATED AFTER PROLONGED STUDIES OF THE PLASMA CONCENTRATION AND DAILY EXCRETION OF VITAMIN C IN THREE ADULTS ON CONTROLLED DIETS. E. P. RALLI, G. J. FRIEDMAN and S. SHERRY, J. Clin. Investigation **18**:705 (Nov.) 1939.

The daily excretion of vitamin C and the plasma concentration of the vitamin were determined for 3 men kept on control diets and fed varying amounts of vitamin C in the form of ascorbic acid.

When less than 100 mg. of vitamin C was fed daily, it was impossible either to raise or to maintain a vitamin C level of 1.0 mg. per hundred cubic centimeters in the plasma. When 50 mg. was fed daily, the plasma concentration of vitamin C averaged 0.5 mg. per hundred cubic centimeters, a level considered the lower limit of normal. It is suggested that 100 mg. of vitamin C be considered the optimum daily intake for adults.

GUEST, Cincinnati.

ASCORBIC ACID CONTENT OF GOAT'S MILK AND BLOOD: INFLUENCE OF ASCORBIC ACID INJECTION AND DIET. MARTHA S. RICHMOND, G. H. SATTERFIELD, C. D. GRINNELLS and W. J. DUNN, J. Nutrition **20**:99 (Aug.) 1940.

In 360 samples of milk taken from five Toggenburg goats receiving a normal diet, the ascorbic acid content titrated between 0.5 and 2 Gm. per hundred cubic centimeters. In 190 samples of blood from these same goats the ascorbic acid content ranged between 0.6 and 0.8 mg. per hundred cubic centimeters. There was no consistent relation between the ascorbic acid content of the blood and that of the milk. After an intraperitoneal injection of 1 or 2 mg. of ascorbic acid there was noted a rapid rise in the ascorbic acid level in the blood and in the urine and a slower small rise in the level of ascorbic acid in the milk. The investigators concluded that apparently the blood level is not closely dependent on the dietary ascorbic acid, suggesting that the goat is independent of a dietary supply of ascorbic acid and that the diet apparently affects the ascorbic acid content of the milk more than that of the blood. The latter conclusions were drawn from observations on 4 other goats fed alternately a diet free of vitamin C and a normal diet.

FREDEEN, Kansas City, Mo.

FURTHER EVIDENCE OF THE MODE OF ACTION OF VITAMIN D. MARGARET CAMMACK SMITH and HARRY SPECTOR, J. Nutrition **20**:197 (Sept.) 1940.

Smith and Spector found that ingestion of liquid petrolatum interfered with both the healing and the prevention of rickets in rats which normally resulted from ultraviolet irradiation. They concluded that this presents further evidence that one role of vitamin D is to increase, either directly or indirectly, the intestinal absorption of calcium or phosphorus.

FREDEEN, Kansas City, Mo.

THE MINIMUM REQUIREMENT OF RIBOFLAVIN FOR THE GROWING PIG. E. H. HUGHES, J. Nutrition **20**:233 (Sept.) 1940.

Hughes concludes that 1 to 3 mg. per 100 pounds is the minimum daily requirement of riboflavin for the young growing pig.

FREDEEN, Kansas City, Mo.

THE MINIMUM REQUIREMENT OF THIAMIN FOR THE GROWING PIG. E. H. HUGHES, J. Nutrition **20**:239 (Sept.) 1940.

Hughes concludes that 1 mg. per 100 pounds is the minimum daily requirement of thiamine chloride for the young growing pig.

FREDEEN, Kansas City, Mo.

DETERMINATION OF VITAMIN C IN CHILDREN BY INTRADERMAL INJECTION. H. G. RAPAPORT and S. H. MILLER, J. Pediat. **15**:503 (Oct.) 1939.

A series of 100 children were given each an intradermal injection of a dichlorophenolindophenol solution, and in each a bluish wheal was produced. The length

of time for the blue color to disappear was noted. The ascorbic acid of the blood plasma was determined, and an attempt was made to correlate the time taken for the dye substance to decolorize with the amount of vitamin C in the blood plasma. No correlation was found which could be used satisfactorily for clinical purposes.

RAUH, Cincinnati.

VITAMIN A STATUS OF CHILDREN AS DETERMINED BY DARK ADAPTATION. J. M. LEWIS and C. HAIG, J. Pediat. **16**:285 (March) 1940.

The purpose of this investigation was to determine the frequency with which vitamin A deficiency is encountered in children. In view of the fact that vitamin A deficiency brings about an elevation in the final rod threshold, i. e., the minimum intensity of light observed by the subject after complete dark adaptation, the authors made use of the final rod threshold level as a criterion of vitamin A deficiency. The final rod threshold was determined in 144 children ranging in age from 6 to 12 years. Sixteen children were private patients, and the remainder were ward or ambulatory patients at Bellevue Hospital. The tests revealed normal threshold values in all but 1 subject. This child had been on a rigorous diet low in vitamin A. Administration of 120,000 units of vitamin A brought about a fall of the threshold value to normal in thirty-five minutes. The effect of this dose lasted twenty days. Then provitamin carotene (120,000 units) was given, and the threshold returned to normal in twenty-two minutes.

FROM AUTHORS' SUMMARY. (RAUH, Cincinnati).

VITAMIN E IN THE TREATMENT OF MUSCULAR DYSTROPHIES AND NERVOUS DISEASES. F. BICKNELL, Lancet **1**:10 (Jan. 6) 1940.

In 1938 it was suggested by Einarson and Ringsted, working on rats in Denmark, that amyotrophic lateral sclerosis and tabes dorsalis, forms of muscular dystrophy, are due to a deficiency of vitamin E. The author gives brief reports of 8 cases of muscular dystrophy—4 of amyotrophic lateral sclerosis, 2 of tabes dorsalis, 1 of peroneal muscular atrophy and 1 of amyotonia congenita.

In the myopathic group—chiefly children—the results of treatment with vitamin E were remarkable. In amyotrophic lateral sclerosis the results were promising.

Normal human diets may be poor in vitamin E. LANGMANN, New York.

DIGESTIVE DISTURBANCE DUE TO DEFICIENCY OF THE FACTORS OF THE VITAMIN B_1 COMPLEX. A. J. ABALLI and A. E. ACES, Bol. Soc. cubana de pediat. **12**:91 (March) 1940.

Aballi and Aces report that in a study of 63 children 43 showed definite or presumptive signs of vitamin B complex deficiency and the other 20, malnutrition, complicated with prolonged gastrointestinal disturbances. These digestive difficulties were treated with vitamins of the B complex.

The majority of children who show definite signs of vitamin B deficiency have gastrointestinal disturbances (anorexia, vomiting, tympanitis and diarrhea). Many show enlargement of the liver and decreased ability to excrete bromsulphalein.

On autopsy slight alterations of the glands of the colon and fatty infiltrations of the liver were found. Occasionally, a process of "serous hepatitis" was observed.

In malnourished children who showed prolonged digestive disturbances the use of vitamin B complex and an adequate diet produced satisfactory results. There was rapid subsidence of diarrhea and anorexia, and gain in weight.

Relapses were infrequent, mild and of short duration and were always brought on by parenteral infections.

Vitamin B complex deficiencies seem to be important as causes predisposing to alimentary intoxication among children of the poorer classes in Cuba. Parenteral

infections cause violent gastrointestinal disturbances in children suffering from such deficiencies. This tendency to toxicosis disappears with adequate vitamin therapy.

SCHLUTZ, Chicago.

TREATMENT OF RESISTANT RICKETS BY MASSIVE VITAMIN D ADMINISTRATION. S. COSTA, Rev. chilena de pediat. **10**:265 (May) 1939.

Costa reports the case of a 13 month old infant suffering from severe and intractable rickets in whom this unusual form of treatment was very successful. On two successive days 10 cc. of viosterol was given. This dose corresponded to 120,000 international units.

Five days after the beginning of this treatment the blood phosphorus rose to 5 mg. and the blood calcium to 13 mg. per hundred cubic centimeters.

Thirty-four days after the beginning of the treatment all symptoms of active rickets had disappeared.

SCHLUTZ, Chicago.

RICKETS—PROPHYLAXIS WITH A SINGLE MASSIVE VITAMIN D ADMINISTRATION. K. SCHWARTZER, Med. Klin. **35**:1657 (Dec. 29) 1939.

Good results were obtained with a dose of 15 mg. Cod liver oil should be administered because of its vitamin A content. General and dietetic antirachitic measures should not be neglected.

SIEMSEN, Chicago.

Hygiene; Growth and Nutrition; Public Health

EFFECT OF CRADLING PRACTICES ON THE ONSET OF WALKING IN HOPI CHILDREN. W. DENNIS and M. G. DENNIS, J. Gen. Psychol., March 1940, p. 77.

This paper deals with the effect of restriction of movement on the motor development of young children. The subjects of study were the infants in two Hopi villages where cradle boards were used almost constantly during the first few months of life. The restraint employed prevents the movement of any part of the body except the head. The infant is placed on the restraining board the first day of life and for the first three months he spends nearly all of his hours in this position. After this the amount of time he is off the board is increased gradually, but his sleep and daytime naps continue to be taken while in the restrained position. All of the infants used the board for at least six months and some for more than a year. The motor development of the cradled children was compared with that of the children of other Hopi villages where cradle restraint was not practiced. Otherwise the two groups of children did not differ in cultural or physical environment. It was found that the cradling practices of the one group had no influence on the age at which walking began, and it was felt that the results of this study were in accord with other recent experimental studies on the relation of training to maturation. It was felt that this not inconsiderable degree of restraint had no influence on the behavior repertoire of these children.

WEINFELD, Highland Park, Ill.

HEALTH OF THE SCHOOL CHILD. Brit. M. J. **1**:142 (Jan. 27) 1940.

This is merely a statistical report of the health officer as to the general state of health of the school children. It does not lend itself to abstracting.

ROYSTER, University, Va.

STATUS OF THE NEUROENDOCRINE SYSTEM AS RELATED TO GROWTH AT VARIOUS AGES OF CHILDHOOD. C. TORRICELLI, Lattante **11**:113 (April) 1940.

Biot and Richard in 1935 reported on the property possessed by isotonic solutions of extracts of the glands of internal secretion in inhibiting the lytic power of human serum toward the red blood cells of sheep.

Torricelli carried this technic into a study of 100 children up to 11 years of age. The glandular extracts studied were from the thyroid, the thymus, the adrenal cortex and the anterior lobe of the hypophysis—the glands which largely have to do with growth.

While the results in general tend to fit it with laws governing growth, the test is not well suited to infants and children, because it is difficult to obtain sufficient serum and because infants' serum has less potency than has adults' serum in hemolyzing sheep red blood cells. HIGGINS, Boston.

THE MEDICAL AND SOCIAL PROBLEM OF COCA IN BOLIVIA. JULIO CESAR PEREZ, Bol. Inst. internac. am. de protec. a la infancia **14**:37 (July) 1940.

The author makes a historical reference to the use of coca, the origin of which is unknown, as well as of the chemical principles which characterize its action, studied and described several centuries ago (1550).

In Bolivia the great majority of the population devoted to rural labors and to work in the mines uses coca daily, chewing the leaves; in these conditions coca produces a decrease in the salivary secretion, an increase in the urinary secretion and dryness of the mouth. It lessens the sensibility of the mucous membranes of the mouth, pharynx and stomach and also lessens appetite; moreover, it exercises an anesthetic action on the peripheral nerve extremities; it produces mental excitement, sleeplessness and headache, with a sensation of general rise of temperature.

On account of the dangerous effects of coca, its use constitutes a serious problem that it is necessary to attack.

The author calls attention to the fact that coca produces in some departments as much as three fourths of the departmental income and that also it increases the fiscal profits with the export duties to such a degree that total suspension of the use of coca would affect seriously the financial budget of the state; under these circumstances the author says that if the cultivation of coca is diminished it should be replaced by the cultivation of coffee, rice, sugar, etc., products which Bolivia has to import at high rates.

If coca were replaced by other products, within some years the present serious eugenic problem would be solved, thus attaining the rejuvenation of the proletarian population, which in Bolivia is gradually diminishing owing to this vice (chewing of coca leaves) and to the hard work in the mines. EDITOR'S SUMMARY.

Prematurity and Congenital Deformities

THE INTRA-UTERINE DEVELOPMENT OF RESPIRATORY EFFORT. JOSEPH BARCROFT, Brit. M. J. **2**:986 (Nov. 18) 1939.

This is a study of intrauterine or embryologic reflexes especially with reference to the respiratory impulse considered from the point of view of both the physiologic and pathologic influences. The article must be read in its entirety to be appreciated. It does not lend itself to abstracting. ROYSTER, University, Va.

MEGALOSOMIAS OR LOCALIZED HYPERTROPHIES OF CONGENITAL ORIGIN. M. SCHACHTER, Rev. franç. de pédiat. **15**:268, 1939.

A brief review of various types of hypertrophy is given. The author then describes a case of symmetric hypertrophy of both arms and of the thumbs and index fingers. Photographs accompany the article. LESLIE, Evanston, Ill.

PREMATURE INFANTS. A. MEIER, Ztschr. f. Kinderh. **61**:355 (Oct. 5) 1939.

At the time of birth reduction of the baby's temperature must be avoided by the use of a lamp or by immersion in a warm bath and transfer to a warmed bed. For a very small infant proper humidification of the air is desirable for tempera-

ture regulation and water loss (the two processes being closely related). Transfer to a hospital can be carried out without loss of heat by the use of a properly heated basket. Until the infant reaches a weight of 1,800 to 2,000 Gm., sweating is not seen, indicating that central regulation of heat is not fully developed until that time. The question is raised whether marked fluctuations in temperature can cause cerebral damage in the form of encephalitis neoatorum (Virchou).

Feeding is discussed at some length. The initial loss of weight is definitely aphysiologic and should be combated as much as is consistent with the infant's welfare. An attempt should be made to approximate the weight gain which would have occurred had the infant remained intrauterine. Breast milk is mandatory for all infants under 2,000 Gm. Even at 2,500 Gm. it is desirable not to give more than one third of the food requirement in the form of cow's milk (acidified). To meet the high mineral requirement colostrum is valuable. Small infusions of Ringer's and dextrose solution (with caffeine or a cardiac stimulant [metrazol] to prevent shock) given one or two times daily are also helpful. Sucking may lead to exhaustion, and cyanosis and tube feeding should be employed liberally. The transfer to bottle feeding should be gradual. Air swallowed during sucking may elevate the diaphragm and cause respiratory embarrassment. Vomiting can sometimes be overcome by a barium sulfate meal.

Because of its tendency to cause diarrhea, viosterol should not be given until the tenth to twelfth week. Cranial softening in the tubera parietales areas, which occurs quite regularly at about the sixth to eighth week, must not be confused with rachitic craniotabes. Unless anemia is more marked than usual, iron medication should not be used, because of its tendency to cause diarrhea.

SIEMSEN, Chicago.

Acute Contagious Diseases

STATE PROCEDURES FOR COMMUNICABLE DISEASE CONTROL. H. EMERSON, Am. J. Pub. Health **29**:701 (July) 1939.

Emerson points out the variations in public health regulations for different diseases in the various states and suggests revision of the regulations to conform to known facts regarding the incubation periods and transmissibility of the diseases.

LIMPER, Louisville, Ky.

MASS IMMUNIZATION AGAINST DIPHTHERIA WITH SORDELLI'S TOXOID AND CONTACT IMMUNIZATION. A. P. LEON, R. H. VALLADAS and F. ESCARZA, Am. J. Pub. Health **29**:720 (July) 1939.

The mortality from diphtheria in Mexico has increased in recent years, and for that reason the authors, epidemiologists of the Department of Health of Mexico, sought a method of rapid mass immunization, preferably by one injection. The material used was Sordelli's toxoid, a modification of alumina-activated toxoid, in the preparation of which the anatoxin is precipitated with sulfuric acid before being activated with aluminum hydroxide. The potency of the preparation used in this study was 10 to 15 L_f units per cubic centimeter.

The doses were 0.5, 1 and 1.5 cc. With 0.5 cc., 61 per cent of the subjects gave negative reactions to the Schick test; with 1 cc., 73 per cent, and with 1.5 cc., about 80 per cent. The reactions became negative twenty days after the injection and were still negative three hundred and seven days after the injection. The percentage of susceptible preschool age children whose reactions became negative was lower than that of school age children immunized with the same doses of toxoid.

The second part of the experiment consisted of combined active and passive immunization of susceptible children who had been in contact with patients who had diphtheria or with carriers, by the simultaneous injection of 1,000 to 1,500 units

of diphtheria antitoxin and 1 to 1.5 cc. of Sordelli's toxoid at different sites. All susceptible ones given an adequate amount of antitoxin gave a negative reaction to the Schick test within twenty-four to seventy-two hours after the injections, and 82.2 per cent still gave negative reactions two months later. Local reactions were observed in 72.7 per cent of the cases and general reactions in 27.5 per cent of the cases.

LIMPER, Louisville, Ky.

THE PERSISTENCE OF VACCINE VIRUS IN RABBITS IMMUNIZED TO VACCINIA BY A PREVIOUS INFECTION AND THE RELATIONSHIP OF IMMUNITY TO LATENT VIRUS. J. M. PEARCE, J. Infect. Dis. **66**:130 (March-April) 1940.

"Vaccine virus was isolated from the testicular tissue of 7 of 10 rabbits that had had a known vaccinal infection 6 to 8 weeks before, and from 3 to 5 infected 17 weeks before. A coexistent postinfectional virus III immunity, which was present in 5 animals of this group of 15, had no demonstrable effect upon the ease or incidence of recovery of vaccine virus.

"No virus could be recovered from 10 rabbits vaccinated 42 weeks earlier.

"All of the 25 animals were immune to vaccinia at the end of the experimental period and no correlation could be demonstrated between persistence of virus and immunity."

TOOMEY, Cleveland. (From Author's Summary.)

STUDIES ON THE MENINGOCOCCUS AND MENINGOCOCCUS INFECTION. N. SILVERTHORNE, J. G. FITZGERALD and D. T. FRASER, with the Technical Assistance of COLIN CAMERON, J. Pediat. **15**:491 (Oct.) 1939.

Fifty-one children with meningococcic meningitis were studied during a seven year period. The mortality rate for the entire group was 42 per cent. All of those with fulminating and chronic basilar disease died. Of the 40 whose disease was acute, 25 per cent died. The environmental conditions of 42 of the group were studied. Ninety per cent of these 42 children came from homes which were poverty stricken. In these homes 327 contacts of the patients were examined for the presence of meningococci in the nasopharyngeal regions, and 31 per cent were found to be harboring meningococci. Ninety-four per cent of the isolated strains were virulent for mice. In 33 of the 42 families one or both parents were found to be harboring meningococci. In a period of four and one half years 2,378 nasopharyngeal cultures were examined from an average of 50 persons monthly. Twenty per cent of these cultures were positive. The majority of the strains isolated from patients, contact carriers and noncontact carriers were type II.

RAUH, Cincinnati.

SOME PROBLEMS OF DIPHTHERIA IMMUNIZATION. M. M. HILLMAN and J. I. LINDE, J. Pediat. **15**:513 (Oct.) 1939.

Three groups of children immunized against diphtheria were studied. The first group was immunized at the age of 6 to 12 months with two doses of unmodified toxoid one month apart. The second group was given a 1 cc. dose of alum-precipitated toxoid at the age of 6 months to 5 years. The third group received two doses of unmodified toxoid at the age of 6 months to 5 years. This group was given the Schick test again after having once been found negative to it. These studies revealed that a greater percentage of infants immunized at 6 months were negative to the Schick test than of those immunized at 1 year when tested six months after immunization. This higher percentage of negative reactions in those immunized at six months is probably not due to the immunity conferred as the result of the administration of toxoid but is due to passive immunity inherited from the mother. The percentage of negative reactions was found considerably smaller among infants tested one year after immunization than among those tested six months after immunization. A 25.5 per cent reversal of negative to positive results

occurred when the children were tested one to five years after the first application of the Schick test. Three doses of unmodified toxoid given at four week intervals was the most effective method of diphtheria immunization. RAUH, Cincinnati.

SUMMARY OF CURRENT PREVALENCE OF COMMUNICABLE DISEASES. Pub. Health Rep. **55**:619 (April 12) 1940.

For the period of Feb. 25 to March 23, 1940, for the first time since this material has been presented in this manner, the incidence of each of the eight contagious diseases was below the median expectancy. The average mortality from all causes was 12.3 per thousand. This is also below the median average.

SANFORD, Chicago.

GEOGRAPHIC DISTRIBUTION OF DIPHTHERIA MORTALITY IN THE UNITED STATES. C. C. DAUER, Pub. Health Rep. **55**:622 (April 22) 1940.

There were 30,000 cases of diphtheria, with 2,600 deaths, in the United States in 1938. This represents a decline of almost 80 per cent in incidence and mortality in two decades. In a map of mortality rates over 10 from 1934 to 1938 a fairly large number of the counties with such rates were found in Virginia, North Carolina, Missouri, Arkansas, Texas and New Mexico. SANFORD, Chicago.

ADMINISTRATIVE FACTORS INVOLVING EFFECTIVENESS OF COMMUNICABLE DISEASE CONTROL. E. A. LANE, Pub. Health Rep. **55**:711 (April 26) 1940.

Data are given to show that unavoidable delay may occur in the control of communicable diseases, as in the visit of a physician, the date of receipt of report, the date of onset and the beginning of control from the health department. It seems doubtful if such delays can be avoided under present conditions.

SANFORD, Chicago.

CEREBROSPINAL PATHOLOGY OF EXPERIMENTAL POLIOMYELITIS IN THE EASTERN COTTON RAT, SIGMODON HISPIDUS HISPIDUS, AND IN THE WHITE MOUSE, MUS MUSCULUS. R. D. LILLIE, Pub. Health Rep. **55**:718 (April 26) 1940.

Intracerebral inoculation with the Lansing strain of poliomyelitis virus produces in cotton rats and white mice a process closely similar to that of poliomyelitis in man and monkeys. In general, the amount of lymphocyte infiltration of vessel sheaths is less in cotton rats than in mice, monkeys and man.

SANFORD, Chicago.

A NOTE ON THE PATHOLOGY IN MONKEYS OF THE LANSING STRAIN OF POLIOMYELITIS VIRUS BEFORE AND AFTER PASSAGE IN THE COTTON RAT. J. H. PEERS, Pub. Health Rep. **55**:726 (April 26) 1940.

After transfer of the virus of poliomyelitis to and during its propagation in rats it has been reinoculated into monkeys. In these the lesions produced were similar to those in the rat. It appears, therefore, that neither the initial transfer nor the subsequent passage through 33 cotton rats visibly modified the pathogenic properties of this strain of virus. SANFORD, Chicago.

TREATMENT OF SCARLET FEVER. H. J. JACOBSON, South. M. J. **33**:774 (July) 1940.

The author reports that many patients with scarlet fever recover spontaneously, without specific treatment. In any patient with a mild attack serious complications may develop, so that specific medication is always in order. Active immunization with scarlet fever toxin should receive serious consideration despite reactions in 10 to 15 per cent of the subjects. It is especially effective in the control of epi-

demics and in hospitals and institutions where the inmates are exposed to the disease. A practical scheme of treatment would be a combination of serum and sulfanilamide with the necessary symptomatic treatment. SCHLUTZ, Chicago.

CEREBRAL ŒDEMA IN SCARLET FEVER. J. B. JESSIMAN, Arch. Dis. Childhood **14**:352 (Dec.) 1939.

A case of cerebral edema occurring in the course of toxic scarlet fever infection is recorded. The complication was an early one and probably resulted from toxemia and from water intoxication. The immediate response to simple and appropriate treatment seems to confirm the diagnosis. KELLY, Milwaukee.

EXPERIMENTAL PERTUSSIS IN THE MONKEY. E. A. NORTH, E. V. KEOGH, R. CHRISTIS and G. ANDERSON, Australian J. Exper. Biol. & M. Sc. **18**:125 (June) 1940.

With suspensions from twenty-four hour cultures of phase I Haemophilus pertussis, intratracheal and intranasal inoculations were made in monkeys. After the intratracheal inoculations the organism could be cultured from the cut surface of the lungs only after the seventh day. After intranasal inoculations the organism could be recovered as early as the third day. However, clinical symptoms, such as cough, were lacking. TANNEY, Madison, Wis.

DIPHTHERIA PROPHYLAXIS: A REVIEW OF THE ANTIGENS AND METHODS AVAILABLE. J. T. LEWIS, Brit. M. J. **2**:1226 (Dec. 23) 1939.

This is a somewhat sketchy statement of the results obtained with the Schick test in children after administration of alum-precipitated toxoid in various doses. ROYSTER, University, Va.

THE ADENOPATHIES AND THE LEUKOCYTIC FORMULA IN MEASLES. R. CROSNIER, Paris méd. **2**:125 (Aug. 12) 1939.

In a study of 200 to 300 cases of measles the author noted moderate general enlargement of the lymph nodes in almost all instances. This may be detected before the occurrence of the cutaneous eruption and is sometimes the only clinical sign present in abortive cases. He also studied the leukocytic picture in about 100 cases and found that leukopenia with monocytosis was the characteristic feature. He feels that the monocytosis reflects hyperactivity of the reticuloendothelial system. LESLIE, Evanston, Ill.

PREVENTION OF PERTUSSIS WITH A VACCINE OF HIGH CONCENTRATION OF BACILLI. E. TATAFIORE, Med. ital. **20**:565 (Dec.) 1939.

The author gave 34 tuberculous children 50,000,000,000 bacilli in a pertussis vaccine in three injections on alternate days (10,000,000,000; 20,000,000,000; 20,000,000,000). These children had been exposed to pertussis for five days. Two of the children had a light attack of pertussis. Only 2 children had a febrile reaction to the vaccine. The 2 patients with pertussis were given an additional 50,000,000,000 bacilli, and the author feels that they were benefited. There were no complications. MARTOCCIO, Utica, N. Y.

EPIDEMIC PAROTIDITIS AND CHOROIDITIS. R. LAJE WESKAMP and CARLOS NOCCALANDRO, Arch. de oftal. de Buenos Aires **14**:193 (Feb.) 1939.

A case is reported in which choroiditis made its appearance just prior to the outbreak of parotiditis. The case is fully studied, with the exclusion of other possible etiologic factors, including Heerfordt's parotiditis, and was complicated with mild meningitis. C. E. FINDLAY. [ARCH. OPHTH.]

ENCEPHALITIS IN THE COURSE OF WHOOPING COUGH. F. BAZÁN and R. MAGGI, Rev. Assoc. méd. argent. **53**:1171 (Dec. 30) 1939.

Bazán and Maggi report their observations made from 1936 to 1939 in the department of infectious diseases of a pediatrics hospital in Buenos Aires, Argentina. Of 600 children with whooping cough, 15 (11 infants and 4 children ranging in age from 3 to 6 years) had acute encephalitis, as a rule in the third week of the illness. The authors found that the course of encephalitis complicating whooping cough varies with the age of the patient, the clinical form and type of encephalitis and the presence or absence of bronchopneumonic complications or otitis. The younger the patient, the graver the nervous complications. These may be acute, subacute or chronic, with predominance of convulsions, somnolence, paralysis, polyneuritis, ataxia, choreoathetosis, poliomyelitis and sensory and psychic disturbances. Convulsive forms are the most frequent. The cerebrospinal fluid either is normal or shows a moderate lymphocytic reaction. The prognosis is grave (a mortality rate of 80 per cent in severe forms of encephalitis and the development of psychic, motor or associated psychomotor sequels in 50 per cent of cases of the subacute form). The condition is due to a toxic infection, the nature and mechanism of which are not clear. The treatment consists of administration of drugs to control convulsions, the general toxic infection and associated infections, baths, antispasmodic drugs, anesthetic, lumbar puncture for the convulsion, methenamine or a combination of cinchophen and methenamine, intravenous administration of hypertonic solution of dextrose, colloidal metals, protein therapy, abscess fixation and sulfanilamide. Associated infections are treated and vaccines against whooping cough are administered according to indications. It is advisable to watch and stimulate the functions of the cardiovascular system and to improve the organic resistance of the patient. If sequels remain, massage, electrotherapy, gymnastics and psychic reeducation are indicated. In the group of cases reported by the authors 12 patients died (all but 1 of whom were infants). Necropsies performed in 9 cases demonstrated that the pathologic lesions are not typical for whooping cough. They consist of degeneration, inflammation and hemorrhages.

J. A. M. A.

POSTDIPHTHERITIC PARALYSIS. J. BULLÓ and H. CERASO, Rev. neurol. de Buenos Aires **4**:55, 1939.

A man aged 22 had severe sore throat; the clinical diagnosis of diphtheria was made and was confirmed bacteriologically. He was given a total of 55,000 units of antitoxin. A week later, there developed difficulty in phonation and deglutition, diplopia and flaccid, painful quadriplegia. The spinal fluid contained 6 cells per cubic millimeter and 0.65 per cent of albumin; the Wassermann reaction was negative. Of particular interest was a study of the fluid for diphtheria toxin and antitoxin; it contained none of either (that is, less than $\frac{1}{300}$ unit per cubic centimeter). At the same time, the blood contained $\frac{1}{30}$ unit per cubic centimeter. The patient made a gradual recovery.

PUTNAM, New York. [ARCH. NEUROL. & PSYCHIAT.]

SULFAPYRIDINE IN TREATMENT OF EPIDEMIC MENINGITIS. W. JÄCKLI, Schweiz. med. Wchnschr. **70**:280 (March 30) 1940.

Treatment of epidemic meningitis at the children's hospital in Zurich consists, according to Jäckli, of oral administration of sulfapyridine in a daily dose of 1 Gm. for each 10 Kg. of body weight. This quantity is distributed evenly over the twenty-four hours at four hour intervals. The medication is continued until the cerebrospinal fluid is clear (from 50 to 150 cells per cubic millimeter) and meningococci are no longer demonstrable, which is usually the case in from two to five days. The dose is gradually decreased and the medication is terminated

between the eighth and the twelfth day. The individual doses at the onset are somewhat larger in order to reach the desired concentration in the blood and cerebrospinal fluid as soon as possible. Lumbar punctures are made twice a day in the beginning, control punctures occasionally. The treatment is often begun with a blood transfusion. Serum is not given. Cardiac and circulatory stimulants are employed according to need. Intramuscular injections of sulfapyridine are employed when oral medication is not tolerated. Administration of sulfapyridine by intravenous drip is another valuable mode. It makes possible the administration at the same time of nutrient substances and fluids. It is reserved for comatose patients and for patients with primary uncontrollable vomiting. The daily dose of soluble sulfapyridine is added to the infusion fluid of a 5.5 per cent solution of dextrose in Ringer's solution. Cardiac and circulatory stimulants may be added to the infusion fluid. The drip infusion is continued only as long as absolutely necessary, usually from two to five days. The author employed this therapy for 16 children with epidemic meningitis admitted during the epidemic of December 1939 to February 1940. The ages of the children varied from 6 months to 15 years. They either were completely cured or had advanced far in their convalescence at the time of the report.

J. A. M. A.

POSTVACCINAL ENCEPHALOMYELITIS. ADELHEID LEIFER, Ztschr. f. d. ges. Neurol. u. Psychiat. **164**:352 (Jan.) 1939.

Leifer reports the case of a girl aged 5 years who died four weeks after vaccination. Three days after the vaccination persistent headaches and body pains developed. The patient then became listless and sleepy. After thirteen days vomiting began, and on the next day she refused food. She was admitted to the hospital fifteen days after the vaccination. She was somnolent and febrile and did not respond to commands or to intense stimuli. The upper limbs were rigid, and the head was turned to the left. There was opisthotonos, with forced conjugate deviation of the eyes to the left. The pupils reacted to light. The radial and periosteal reflexes were more active on the right than on the left; the abdominal reflexes were not obtained; the knee and ankle jerks were equally active on the two sides; the left plantar reflex was of the Babinski type; a mild Kernig sign was elicited on both sides; there were abnormal movements of the whole right upper limb. Lumbar puncture revealed a pressure of 300 mm. of water, with 74 cells, of which 73 were lymphocytes. There were 13,700 white cells in the blood, with 92 per cent polymorphonuclear cells. The sugar content of the spinal fluid was 66 mg. per hundred cubic centimeters. Choreiform movements in the right upper limb persisted. A facial tic appeared. The child died one month after vaccination.

Areas of demyelination and perivascular accumulations of cells were scattered throughout the brain and cord. The white substance of the cerebral hemispheres, the brain stem and the cord was involved, as well as the gray matter of the cortex, the cord and the basal ganglia. The center of the areas of involvement was always a vein. The perivascular cells were glial, mainly gitter cells and more rarely rod cells and astrocytes. Ganglion cells in the affected areas were spared. No periarterial foci were seen. The axons were relatively preserved. Leifer noted the presence of subependymal foci near the lateral ventricles and subpial lesions in the cord. There was rather marked disturbance in the cytoarchitectonics of the cortex in the region of the cornu ammonis and in the occipital area. There was considerable dropping out of ganglion cells. These changes were similar to those described by Spielmeyer in cases of convulsions associated with pertussis, and have been considered as due to vasomotor spasm.

SAVITSKY, New York. [ARCH. NEUROL. & PSYCHIAT.]

Acute Infectious Diseases

PROGNOSIS IN JUVENILE RHEUMATIC FEVER. STANLEY GIBSON, Illinois M. J. **78**:341 (Oct.) 1940.

In this study of 1,487 patients with rheumatic fever and chorea, 864 showed signs of heart disease. One hundred and forty-six of the patients died. Rheumatic nodules and pericarditis occurred in a much higher percentage of those who died than of those who survived. Chorea and rheumatic erythema were most frequently associated with mild rheumatic infection. Polyarthritis was the most frequent rheumatic manifestation. Rheumatic nodules usually occurred in association with active rheumatic heart disease. Pericarditis was a serious manifestation of rheumatic heart disease.

BARBOUR, Peoria, Ill.

CLINICAL MALARIA IN CHILDREN. C. D. WILLIAMS, Lancet **1**:441 (March 9) 1940.

This report on malaria in children comes from the King Edward VII College of Medicine at Singapore.

The author distinguishes four clinical types: 1. Acute malaria with parasites present and distinct symptoms. 2. Chronic malaria with parasites present. 3. Chronic malaria in children from a malarial country in whom no parasites can be found but who improve under adequate treatment with quinine. 4. Presence of malarial parasites in blood of children apparently normal and healthy in every way.

The manifestations of malaria are just as various in infants and children as they are in adults. The first attack of malaria is generally the worst. Anemia and convulsions are more common, more severe and more sudden than in adults.

Treatment with quinine sulfate and iron is advocated. Intramuscular injections of quinine are often of value particularly if gastrointestinal disturbances hinder the absorption of quinine given by mouth. In a malarial country attacks of fever are very common in babies aged 6 to 18 months. Children taken to a malarial country should be protected from mosquitoes. Prophylactic quinine is not advised by all authorities, but it probably does some good. Adequate treatment early in the disease is most important. Treatment with quinine does not appear to interfere with the development of immunity.

LANGMANN, New York.

TETANUS: PROPHYLAXIS AND TREATMENT. L. ROUQUÈS, Presse méd. **48**:497 (May 15-18) 1940.

By May 1939, about 1,500,000 persons in France had been given tetanus toxoid. The Italian and British armies have also been given tetanus toxoid. So far no case of tetanus in the immunized soldiers has been reported. The use of tetanus toxoid has also apparently eliminated tetanus in horses.

Wounded men who have received toxoid are given another dose to augment their protection. If the wounds are extensive or if there is a doubt as to previous protection, antitetanic serum is also given. If tetanus actually develops, antitetanic serum is given, together with toxoid (which will prevent delayed symptoms from the spores which are not attacked by the primary dose of serum).

DAFFINEE, Boston.

VALUE OF ERYTHROSEDIMENTATION IN ARTICULAR RHEUMATISM. M. ACUNA and A. PUGLISI, Arch. argent. de pediat. **12**:247 (Sept.) 1939.

Erythrosedimentation is a valuable guide in acute articular rheumatism of childhood. It gives some indications regarding the intensiveness of the attack and also provides a valuable index of its evolution. The determinations should be carried out in a series.

The type of treatment and of prognostic prediction in the case will depend somewhat on the behavior of the sedimentation rate. Absence of rheumatic manifestations will coincide with a normal sedimentation rate. The return of the latter to normal augurs well for the patient and justifies cessation of all treatment and permission of limited activity.

SCHLUTZ, Chicago.

BACILLARY DYSENTERY IN THE TROPICS. C. J. WYCKERHELD BISDOM, Maandschr. v. kindergeneesk. **9**:143 (Jan.) 1940.

In this article a description is given of 118 cases of bacillary dysentery observed in the Dutch East Indies, subdivided into four groups according to the clinical features. In the first group were more than half of the total number—68 cases. The progress is mild and without complications. In the second group were 30 complicated cases. Special attention is drawn to the serious toxic state which appears a few hours after the beginning of the illness. This state of toxemia is not caused by exsiccosis but by bacterial infection. In the third group were 15 cases of dysentery complicated by convulsions or other symptoms of cerebral irritation. In the fourth group were the disastrous cases rapidly progressing to a fatal end. The clinical aspect is here entirely dominated by the exceedingly serious toxic phenomena, so that often one even forgets to think of the possibility of bacillary dysentery. The patients all died within twenty-four hours. The clinical similarity with the Waterhouse-Friderichsen syndrome has to be borne in mind. The therapeutic measures are discussed. Besides the dietetic treatment, abundant administration of fluid orally, intravenously and eventually by clysis is of the utmost importance. The advantages of serum injections are considered, and other therapeutic measures are mentioned.

VAN CREVELD, Amsterdam, Netherlands.

BACTERIOLOGY OF DYSENTERIA BACILLARIS. A. C. RUYS, Maandschr. v. kindergeneesk. **9**:165 (Jan.) 1940.

For the bacteriologic diagnosis of bacillary dysentery the desoxycholate-citrate culture of Leifson is a great improvement. Bacteriologic examination in cases of bacillary dysentery always should be performed as well to obtain an exact diagnosis and to combat the disease adequately.

VAN CREVELD, Amsterdam, Netherlands.

Chronic Infectious Diseases

THE ORAL TREATMENT OF CONGENITAL SYPHILIS: AN EDITORIAL. Am. J. Syph., Gonor. & Ven. Dis. **24**:117 (Jan.) 1940.

This is a discussion of the value of the oral treatment of congenital syphilis. The pros and cons are well considered. The consensus is summed up in the following paragraph of the article.

"The consensus seems to be that acetarsone is a drug which, if given properly, yields good results in the treatment of congenital syphilis in the infant. It is regrettable that in rural districts where, because of distance or other factors, regular attendance at a clinic station is a hardship, the use of acetarsone is necessarily limited because of the factor of uncertainty of proper administration."

ROYSTER, University, Va.

POTENTIAL DANGERS OF TUBERCULIN TESTS. E. M. LINCOLN and W. GRETHMANN, J. Pediat. **15**:682 (Nov.) 1939.

All tuberculin tests are based on the change in the reaction of the tissues which follows infection with the tubercle bacillus. This reaction is known as the Koch

phenomenon. Besides the reaction which occurs at the site of the injection of tuberculin, there may be a perifocal inflammatory reaction surrounding an existing tuberculous lesion, which may result in progressive tuberculosis. Previous studies have shown that a constitutional reaction may follow the Mantoux test. The latter two reactions have been found to be more common in subjects over the age of 4 years and more common when 0.1 mg. is given than when the test is made with 0.01 mg. Tuberculin is safer to use if lesions are well stabilized, even though extensive, than if the lesions are progressive or active, however small. Seven cases are presented to illustrate the intense focal reaction around an existing tuberculous lesion which may follow the Mantoux test. Lincoln and Grethmann recommend the use of a maximum initial dose of 0.01 mg. of tuberculin for the test. They discourage the custom of repeating the tuberculin test after a positive reaction, for no definite proof has ever been advanced that the size or the character of the local reaction is of help in determining either the location or the morphologic character of the tuberculous lesion.

RAUH, Cincinnati.

THE TREATMENT OF CONGENITAL SYPHILIS. E. F. NAEF. South. M. J. **33**:691 (July) 1940.

Naef presents a small series of cases of congenital syphilis in which treatment was by continuous alternating courses of sulfarsphenamine and bismuth.

All offspring of mothers who present serologic or clinical evidence of syphilis should have a Wassermann test of the blood every month for the first five months of life, and at the termination of that time a Wassermann test of the spinal fluid should be made before declaring the infant nonsyphilitic. The development of any suspicious clinical manifestation of syphilis in the infant is sufficient justification for continuous antisyphilitic treatment, regardless of serologic reactions.

The older the patient at the time of discovery of the prenatal syphilitic infection, the greater the difficulty in obtaining a serologic response to treatment, though clinical improvement is anticipated at any age in childhood. Absence of clinical signs or symptoms should never be accepted as sufficient grounds for deferring further investigation for the presence or absence of syphilis in the newborn whenever a suspicion of parental infection arises.

The author believes that success in the treatment of congenital syphilis is dependent largely on the amount rather than on the type of arsenical administered, provided treatment is continuous, and courses of bismuth are alternated with courses of the selected arsenical.

SCHLUTZ, Chicago.

THE PROBLEM OF THE VIRULENCE OF THE TUBERCLE BACILLUS. W. T. MUNRO, Edinburgh M. J. **47**:110 (Feb.) 1940.

Munro reports 46 postmortem examinations of tuberculous tracheobronchial lymph node infection in children; 34 revealed the human type of tubercle bacilli, 10 the bovine type and 2 a mixture of types. This has significance because of the higher fatality of bovine tuberculosis. In 50 instances of meningeal tuberculosis, the infection proved to be of human origin in 32 and of bovine origin in 18. About the same relation was found in the material from gastric lavage in 35 instances, the infection being of human origin in 21 and of bovine origin in 14.

Tubercle bacilluria was found in 20 of 85 children investigated for tuberculosis. Most of the children with the bovine type of bacilli gave this type also in gastric lavage while every child with a proved infection of the bovine type involving a bone or joint had the same type of bacilli in the urine. The author believes that the bovine type of bacilli in children as well as in adults with pulmonary tuberculosis is disseminated more easily and produces more lesions than the human type.

NEFF, Kansas City, Mo.

TONSILS, ADENOIDS AND TUBERCULOSIS IN PEDIATRIC PRACTICE. R. LIÈGE, Progrès méd., April 27, 1940, p. 351.

Tuberculous meningitis developing two weeks after tonsillectomy and adenoidectomy is reported. Varying statistics are given concerning the presence of tubercle bacilli and tuberculous lesions in the tonsils and adenoids. The author concludes that the possibility of dissemination of tubercle bacilli should be considered in advising for or against tonsillectomy and adenoidectomy.

LESLIE, Evanston, Ill.

PROPHYLAXIS AND TREATMENT OF TUBERCULOSIS IN CHILDREN. R. JEMMA, Med. inf., Rome **10**:321 (Nov.) 1939.

This article is a reprint from Prof. Jemma's *Manuale di pediatria* (Milan, Società editrice libraria, 1938).

Prophylaxis against tuberculosis is obtained (1) by preventing infection, (2) by increasing the resistance of the child and (3) by producing active specific immunity. The treatment of tuberculosis resolves itself into the employment of hygienic, physical and mechanical means, vaccines and drugs.

HIGGINS, Boston.

TUBERCULIN SKIN TESTS IN THE CLINICS OF THE NATIONAL PROJECT FOR THE PROTECTION OF MOTHERS AND CHILDREN. A. BERARDI, Med. inf., Rome **10**:337 (Nov.) 1939.

Tuberculin tests afford protection to the Italian people against the dangers of tuberculosis.

HIGGINS, Boston.

CLINICAL AND EPIDEMIOLOGIC CONSIDERATIONS OF TUBERCULOSIS IN INFANCY. G. ARÁOZ ALFARO, Rev. méd. latino-am. **25**:103 (Nov.) 1939.

The attack on tuberculosis should begin in infancy when the source of the contagion is in the family. Children of tuberculous parents are not more susceptible; in fact, when they are "tubercularized" the reaction is frequently mild, as if they inherited a certain resistance. The primary infection is generally asymptomatic. The early pulmonary lesion may escape detection with the roentgen rays. Instead of gastric lavage for the detection of the Koch bacillus, laryngeal swabs are recommended. The younger the child, the more difficult it is to separate the first two stages of the disease. Aside from general hygienic measures in treatment, calcium and vitamin C may be given subcutaneously. In a case of acute pulmonary disease, if the roentgenogram does not show frank regression, pneumothorax is advised.

DWYER, Kansas City, Mo.

Diseases of Blood, Heart and Blood Vessels, and Spleen

CONGENITALLY DOUBLE LEFT AURICLE. J. B. MCLESTER, J. D. BUSH and J. S. DUBOIS, Am. Heart J. **19**:492 (April) 1940.

The authors were able to find 11 cases of congenitally double left auricle described in the literature and have added 1 case of their own. The autopsy in their case revealed a complete diaphragm dividing the left auricle into an upper posterior portion and a lower anterior portion. Two small slits in this diaphragm permitted the passage of blood. The effect on the circulation was comparable to that which occurs in advanced mitral stenosis.

GIBSON, Chicago.

THE MAGNESIUM CONTENT OF THE ERYTHROCYTES IN PERNICIOUS AND SOME OTHER ANEMIAS. O. BANG and S. L. ØRSKON, J. Clin. Investigation **18**:497 (Sept.) 1939.

An increased magnesium content of the red blood cells is often, but not always, found in anemias from various causes, probably indicating a relative preponderance

of young cells. In pernicious anemia, high magnesium values are found during relapse in the majority of the cases examined, while a decrease toward normal values takes place during remission. These findings support the view that a short lifetime of the red cells plus a concomitantly increased rate of destruction is a decisive factor in the development of pernicious anemia.

FROM THE AUTHORS' SUMMARY.

CLINICAL STUDIES OF THE BLOOD VOLUME: VIII. MACROCYTIC AND HYPOCHROMIC ANEMIAS DUE TO CHRONIC BLOOD LOSS, HEMOLYSIS AND MISCELLANEOUS CAUSES, AND POLYCYTHEMIA VERA. J. G. GIBSON 2D, A. W. HARRIS and V. W. SWIGERT, J. Clin. Investigation **18**:621 (Nov.) 1939.

In chronic anemias, regardless of etiology, plasma volume is above, and circulating red cell and total blood volume are below, normal. During recovery the relation between the increase in circulating red cell volume and the decrease in plasma volume is such that the total blood volume slowly increases, returning to within normal limits when recovery is complete. For clinical purposes the hematocrit level is a better criterion of the degree of deficit in the circulating red cell volume than the red cell count or the hemoglobin value.

FROM THE AUTHORS' SUMMARY.

THE RELATIONSHIP BETWEEN THE ERYTHROCYTE SEDIMENTATION RATE AND THE PLASMA PROTEINS. M. W. ROPES, E. ROSSMEISL and W. BAUER, J. Clin. Investigation **18**:791 (Nov.) 1939.

The erythrocyte sedimentation rates and the plasma protein fractions were determined in 89 blood samples from patients with various diseases. No absolute correlation was found between the sedimentation rate and any of the plasma protein fractions. At least one third of the findings were not consistent with a linear relation between the fibrinogen concentration and the sedimentation rate.

FROM THE AUTHORS' SUMMARY.

EFFECT OF SULFANILAMIDE ON THE CROSS MATCHING OF BLOOD. S. KREININ, J. Lab. & Clin. Med. **25**:690 (April) 1940.

The conclusion reached by Kreinin is that inability to cross-match blood after the administration of sulfanilamide is due to the disease requiring the use of sulfanilamide rather than to the drug itself. READING, Galveston, Texas.

TRAUMATIC RUPTURE OF THE SPLEEN IN CHILDREN, WITH SPECIAL REFERENCE TO LEFT SHOULDER PAIN. N. A. ANDERSON, J. Pediat. **15**:535 (Oct.) 1939.

Anderson reports on 10 children who suffered traumatic rupture of the spleen. The ages of these children ranged from 5 to 15 years, and all but 3 were boys. The most common symptoms of splenic damage were abdominal pain and tenderness. Pain in the left shoulder was an important symptom in 5. Splenectomy was performed in 9; 1 child died before operation could be performed; 2 children died postoperatively. From a review of the literature and her own observations Anderson notes that removal of the ruptured spleen offers a favorable prognosis and causes no demonstrable effect in after life. RAUH, Cincinnati.

DIAGNOSIS AND THE EFFECTS OF LIGATION OF THE PATENT DUCTUS ARTERIOSUS: A REPORT OF ELEVEN CASES. L. T. BULLOCK, J. C. JONES and F. S. DOLLEY, J. Pediat. **15**:786 (Dec.) 1939.

A review of 76 cases of patent ductus arteriosus from the literature and 4 others revealed that 50 per cent of the patients had died by the age of 30 years

and 71 per cent by the age of 40 years. Fifty-three per cent of the patients died of subacute bacterial endocarditis, 86 per cent as the result of the congenital lesion.

This report deals with the results obtained by ligation of the patent ductus arteriosus in 11 patients ranging in age from 4 to 31 years. The criteria used in the selection of the patients for this operation are given in detail. One patient died forty-eight days after the operation, from bacterial endarteritis of the ductus and of the adjacent pulmonary artery, and the other 10 patients at the time of this report were entirely relieved of their cardiac lesion. The blood pressure returned to normal after a short postoperative rise. The thrill and the accentuated pulmonary second sound disappeared. In 6 patients a soft, purely systolic murmur remained at the pulmonic area, while in 5 the murmur disappeared completely. The preoperative symptoms of weakness, palpitation, fatigue and dyspnea disappeared. The oldest patient, who had been bedridden, was able to return to normal activity without symptoms. The children were able to return to unrestricted activity without distress.

RAUH, Cincinnati.

INFECTIOUS MONONUCLEOSIS. A. BERNSTEIN, Medicine **19**:85 (Feb.) 1940.

Infectious mononucleosis is most common in children and young adults, is more frequent in males than in females, and occurs most commonly in the spring and fall seasons. The incubation period averages about eleven days.

Common clinical features of the disease are sore throat, painful neck, abdominal pain, constipation, fever, bradycardia, splenomegaly and lymphadenopathy. The latter is especially evident in the cervical chain, and may precede, accompany or follow fever and other symptoms. Many other symptoms may occur. The uncomplicated disease is never a cause of death.

The typical blood picture of infectious mononucleosis is that of moderate leukocytosis (10,000-20,000) with a marked increase in the percentage of mononuclear cells—large and small lymphocytes and the abnormal "leucocytoid" lymphocytes, characteristic of the disease. Anemia is uncommon. A falsely positive Wassermann test is rather common. The cerebrospinal fluid may show changes whether or not meningitic signs are present. Throat cultures and smears may show streptococci or Vincent's organisms, but usually the flora is indifferent.

The heterophil sheep cell agglutination test was discovered accidentally by Paul and Bunnell and reported in 1932. Except for increased sheep cell antibodies in horse serum-treated persons, the test is rarely positive in diseases other than infectious mononucleosis.

It seems fairly certain that the disease is a systemic infection, but the etiologic agent is unknown. The author thinks the organism may prove to be a protozoan, and states that monkeys are the most promising experimental animal.

Treatment is symptomatic. If a complicating streptococcic infection is present, sulfanilamide should be used. He uses sodium perborate mouth washes prophylactically.

LIMPER, Louisville, Ky.

EXPERIMENTAL LEUCOCYTOSIS IN MAN. N. G. NORDENSEN, Quart. J. Med. **8**:311 (Oct.) 1939.

Nordensen studied the effects of sodium nucleinate, pentose nucleotide and adenine sulfate on the peripheral blood and the bone marrow of 43 patients. Both sodium nucleinate and pentose nucleotide induced continuing peripheral neutrophilic leukocytosis, provided the bone marrow had not been previously damaged. The regulation of the maturation of the myeloid cells in the bone marrow is discussed.

BRADFORD, Rochester, N. Y.

IRON-RESISTANT ANAEMIA AND LATENT RICKETS IN SCHOOL CHILDREN. S. TAYLOR and N. CROWLEY, Arch. Dis. Childhood **14**:317 (Dec.) 1939.

In 12 children, aged between 6 and 12½ years, iron-resistant hypochromic or orthochromic anemia was found, associated with low inorganic phosphorus in the blood but with no definite clinical sign of rickets. Vitamin D, given in two single doses of 200,000 international units at fortnightly intervals, restored the blood phosphorus values to normal in one month but had no effect on the hemoglobin values. A combination of similar doses of vitamin D and ferrous sulfate, 5 grains (0.3 Gm.) twice a day, raised the mean hemoglobin readings from 79 to 89 per cent in one month.

KELLY, Milwaukee.

THE ELECTROCARDIOGRAM IN CONGENITAL CARDIOPATHIES: PROLONGATION OF THE DURATION OF THE RAPID WAVE AND RIGHT BRANCH BLOCK. D. ROUTIER, J. BRUMLIK and A. MALINSKY, Arch. d. mal. du cœur **33**:40 (Jan.-Feb.) 1940.

Twenty-three cases of right ventricular preponderance and right branch block of the type described by Van Deesten and Dolganos and by Wilson are discussed in this paper. The QRS complex was in excess of 0.10 second in all these cases, the time spread being from 0.11 to 0.18 second, inclusive. Notching of the rapid wave in lead II was almost constant in the electrocardiographic tracings.

Grouping their patients according to age (14 to 59 years), the authors believe that prolongation of the QRS is a characteristic acquired in the course of progress of congenital cardiopathies affecting the right ventricle rather than a congenital characteristic.

The authors hold that prolongation of the duration of the QRS in congenital cardiopathies points against the diagnosis of interventricular communication and in favor of that of interauricular communication.

TURNER, Chicago.

INFECTIOUS RETICULOENDOTHELIOSIS (ABT OR LETTERER-SIWE DISEASE) AND ITS RELATION TO SCHÜLLER-CHRISTIAN DISEASE. E. GLANZMANN, Ann. pædiat. **155**:1 (April) 1940.

So-called infectious reticuloendotheliosis (Abt; Letterer-Siwe) is probably no morbus sui generis but a syndrome (purpura, adenopathy, hepatosplenomegaly and hypochromic anemia). This syndrome is closely connected with Schüller-Christian xanthomatosis with pituitary "geographic skull" and other skeletal changes and probably represents the acute septic form of the disease in early infancy.

There are transitory forms between infectious reticuloendotheliosis and Schüller-Christian disease. Among them should be classified the conditions observed by Schulz, Wermbter and Puhl and the infectious reticuloendotheliosis described by Glanzmann, occurring in an illness which is obviously very similar to Schüller-Christian disease and is only transitory.

The Letterer-Siwe syndrome occurs also in proved cases of lipoid granulomatosis, as in the cases of Attig and Ighenti and of Rietschel.

The syndrome probably represents a special and peculiar form of reaction of early infancy to a streptococcic infection.

FROM AUTHOR'S SUMMARY.

A CASE OF CONGENITAL HEART BLOCK WITH PAIN IN THE SHIN BONES. H. WISSLER, Ann. pædiat. **155**:53 (April) 1940.

Wissler describes a case in which heart block was discovered at the age of 5½ years by chance. At the same time clinical signs of a septum defect were found. No marked bradycardia was noted. Peculiar and obstinate pains were present over both tibias, which may have been due to a very slight form of "ostéoarthropathie pneumique hypertrophiante" (Pierre Marie).

FROM AUTHOR'S SUMMARY.

Diseases of the Nose, Throat and Ear

HEARING ACUITY AND STAMMERING. M. A. HARMS and J. Y. MALONE, Ann. Otol., Rhin. & Laryng. **48**:658 (Sept.) 1939.

It is estimated that at least 1,000,000 children have speech defects, a number which exceeds that of the crippled, blind and deaf combined. About 10 per cent of those with defective speech are stammerers. Speech is learned by hearing speech. Stammering is rare among children who suffer from total deafness. Poor hearing causes distortion of words and uncertainty as to pronunciation and consequently hesitancy in speech. Stammering becomes more frequent in those with around 50 per cent loss of hearing. Of 62 consecutive stammerers who were unaware of any loss of hearing, a deficiency of hearing was found with the audiometer in from 10 to 22 per cent, strongly suggesting a relation between the loss of hearing and the development of stammering.

M. V. MILLER, Philadelphia. [ARCH. OTOLARYNG.]

RADICAL MASTOIDECTOMY: ITS USE IN TREATMENT OF DANGEROUS TYPES OF SUPPURATION OF THE TEMPORAL BONE. NATHAN A. BOLOTOW, Arch. Otolaryng. **29**:269 (Feb.) 1939.

Twenty-six cases in which radical mastoidectomy was performed are outlined, with emphasis on the importance of the antecedent history in diagnosis, thorough clinical investigation and operation when there is evidence of chronic suppuration which might subsequently endanger the patient's life and cause serious intracranial complications.

GREENWOOD, Chicago.

SULFANILAMIDE THERAPY FOR ACUTE OTITIS MEDIA AND ACUTE MASTOIDITIS. DANIEL C. BAKER JR. and GEORGE E. BRADFORD, Arch. Otolaryng. **29**:334 (Feb.) 1939.

The authors discuss the present value of sulfanilamide in otologic practice, contending that it is of definite importance in all cases of acute otitis media resulting from a hemolytic streptococcus in which hospitalization is required and of probable value in cases in which the condition is due to other organisms.

GREENWOOD, Chicago.

CONGENITAL ABSENCE OF ONE TONSIL; MICROTIA AND POLYDACTYLISM IN THE SAME PATIENT. J. W. GERRIE, Arch. Otolaryng. **29**:378 (Feb.) 1939.

The author presents the case of an 8 year old girl in whom an attack of acute otitis and mastoiditis in a deformed ear revealed an unusual and interesting group of congenital deformities.

GREENWOOD, Chicago.

VALUE OF ENCEPHALOGRAPHY IN THE DIAGNOSIS OF OTOGENIC INTRACRANIAL COMPLICATIONS. ROBERT DINOLT, Arch. Otolaryng. **31**:431 (March) 1940.

Routine encephalographic examination is essential in differentiating (1) swelling of the brain, (2) edema of the brain, (3) serous meningitis and (4) nonsuppurative encephalitis from abscess of the brain. If performed at the proper time, such an examination may obviate the need of surgical cerebral exploration. An illustrative case is presented. A second case, with favorable prognosis, in which papilledema of 6 D. ceded to normal conditions is also reported.

GREENWOOD, Chicago.

CONGENITAL FISTULA OF THE NECK COMMUNICATING WITH THE MIDDLE EAR. JOSEPH G. DRUSS and BENJAMIN ALLEN, Arch. Otolaryng. **31**:437 (March) 1940.

The case of a 5 month old girl with a congenital lateral fistula of the neck communicating with the middle ear is presented. Detailed microscopic studies are included. Other congenital malformations of the external and middle ear, including fistula of the auricle, are discussed.

GREENWOOD, Chicago.

INHALATION OF MASSIVE AMOUNTS OF VEGETAL FOREIGN BODIES. W. A. MCNICHOLS, J. A. M. A. **113**:2055 (Dec. 2) 1939.

A very dramatic story is told of a 7 year old girl who jumped into a bin of ground grain and was submerged about ten minutes. Unconscious and cyanotic, she was given artificial respiration and oxygen. A dry tracheotomy was done, but nothing was inserted in the larynx. About 4 drachms (7 Gm.) of grain were removed with a bronchoscope. With continued aspiration and the use of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) for the subsequently developing pulmonary infection, complete cure resulted.

HEERSMA, Kalamazoo, Mich.

CHRONIC STRIDOR IN INFANCY. J. E. BOWMAN and C. L. JACKSON, J. Pediat. **15**:476 (Oct.) 1939.

Thirty infants seen consecutively because of stridorous breathing form the basis of this report. Fourteen were found to have "congenital laryngeal stridor," i. e., supraglottic obstruction to inspiration due to deformity or flaccidity of the epiglottis, arytenoids and/or aryepiglottic folds. Characteristic of this group is onset of the stridor at birth. In 5 infants the noisy breathing appeared to be due to pressure of an enlarged thymus on the trachea. Lateral roentgenograms of the chests of these 5 infants demonstrated kinking, narrowing and backward displacement of the trachea by a shadow posterior to the manubrium of the sternum. Endoscopic examinations in all 5 revealed nothing of importance. The onset of symptoms occurred at the second or third month, and definite improvement in the stridor occurred within forty-eight hours after roentgen treatment. In 3 infants congenital malformations of the larynx other than those present in the first group were found. Satisfactory study of a child with stridor should include careful roentgen examination of the neck and chest in both planes and endoscopic examination of the larynx and trachea.

RAUH, Cincinnati.

AN ORIGINAL METHOD OF OBTAINING SPUTUM FROM INFANTS AND CHILDREN WITH REFERENCE TO THE INCIDENCE OF PNEUMOCOCCI IN THE NASOPHARYNX. W. J. AUGER, J. Pediat. **15**:640 (Nov.) 1939.

A suction method is described for obtaining sputum from the larynx or from the nasopharynx. For laryngeal suction, the apparatus consists of a 50 cc. syringe, a piece of soft rubber tubing with a small hole cut in one side (so that the thumb can easily cover the hole and act as a valve), a glass tube, a piece of slightly curved stiff rubber tubing or a stiff rubber throat catheter with a notch cut in each side of the tip. The piece of soft rubber tubing is slipped over the tip of the syringe and is connected to the catheter with the glass tube. For obtaining sputum from the nasopharynx, the catheter is replaced by a rubber tube, the diameter of which depends on the size of the child's nares. The barrel of the syringe is held with the left hand, with the thumb covering the hole of the valve. The right hand inserts the catheter toward the uvula until the child coughs or gags. The right hand then grasps the syringe plunger, and suction is commenced. The piston is pulled out with the right hand, while the left thumb covers the hole in the soft rubber tube. At the end of the upstroke, the left thumb is removed and the piston shoved back into the barrel. In this manner, the sputum is not returned into the throat. This motion of repeated in and out stroke of the plunger is continued rapidly until the sputum is seen to rise into the glass tubing. For aspiration of nasopharyngeal sputum the catheter is passed through the nares until it is judged to have reached the adenoid area. Laryngeal sputum is recommended in cases of suspected tuberculosis, pertussis or pneumonia due to mixed infection, while sputum from the nasopharynx is ideal if pneumococci are to be typed. Auger believes the nasopharynx is a breeding ground for pneumococci and the probable source from which pneumococci reach the lung when pneumonia occurs in infants and children.

RAUH, Cincinnati.

THE CLIMATIC FACTOR IN PRECIPITATING ACUTE TONSILLITIS IN CHILDREN. N. D. FABRICANT, J. Pediat. **15**:697 (Nov.) 1939.

The precipitation of acute tonsillitis in children most often takes place in the wake of a "cold front," i. e., when the temperature of the air falls, the barometric pressure increases, and there is lessened humidity. At this time there is a change in the functional status of the mucous membranes of the nose and throat. A latent period or "lag" of a few hours to one or more days may occur before the actual initiation of the clinical symptoms. Nineteen cases of acute tonsillitis in children, each child sufficiently ill to warrant hospitalization, are presented to illustrate the significance of the onset of the "cold front" in precipitating the disease.

RAUH, Cincinnati.

RESPIRATORY INFECTIONS: INCIDENCE AND CLINICAL COURSE AS OBSERVED IN A FLORIDA PEDIATRIC PRACTICE. W. W. QUILLIAN, J. Pediat. **15**:704 (Nov.) 1939.

Quillian reviewed approximately 1,000 hospital records and a similar number of records of private patients who had been seen at the office or at home. He found that 47 per cent of a pediatric practice in Florida is concerned with respiratory infections. This high incidence may be influenced by the seasonal influx of tourists and other factors generally observed in a resort center. The combined clinical experience of several pediatricians of the Miami area confirmed the impression that these respiratory infections are of about the same average duration but less virulent in their course than similar infections occurring in other parts of the country. Complications were found to occur infrequently. The combined mortality rate for both groups of patients in this series was 4.87 per cent.

RAUH, Cincinnati.

CHRONIC SINUS INFECTION IN CHILDREN. P. A. MCLENDON and R. R. RATHBONE, South. M. J. **33**:366 (April) 1940.

The authors state that chronic sinus infection is frequently encountered in children. It follows acute infections of other portions of the respiratory system as well as recurrent attacks of allergic rhinitis. The symptoms are referable not only to the nose and throat but to other systems of the body. The management of the child and the decision as to the type of treatment should be relegated to the family physician or pediatrician. Roentgen therapy is valuable in properly selected cases.

SCHLUTZ, Chicago.

NASAL SINUSITIS IN CHILDREN. D. GUTHRIE, Brit. M. J. **1**:84 (Jan. 20) 1940.

This subject is discussed generally, and the following debatable points are raised:

1. Should routine lavage of the maxillary sinus be practiced at tonsil-adenoid operations?
2. Is the sinus a focus of infection giving rise to arthritis, anemia, nephritis and other disabilities in children?
3. What are the best lines of general treatment—dietetic, climatic, medicinal?
4. Of what relative value are the various local applications?
5. To what extent does roentgenography assist in diagnosis?
6. When is operation to be advised, and is radical operation justifiable?

An account is given of the anatomy and development of the nasal sinuses. The frequency of sinusitis in children and its clinical manifestations are discussed. The cardinal rules to be observed in treatment are laid down, and various methods described.

ROYSTER, University, Va.

DESTRUCTIVE FIBROUS OSTEITIS OF THE FRONTAL SINUS. F. VENTURA-GREGORINI, Arch. ital. di otol. **51**:303 (June) 1939.

Excepting the benign osteoma, a primary neoplasm of the frontal sinus is rare. After reference to the studies of a number of investgators, to the wide divergence between the clinical course and the histologic picture in many cases and to the difficulty of differentiating between benign and malignant growths, the author reports a case of fibrous osteitis of the left frontal sinus in a boy aged 11 years. At operation, it was noted that the anterior and posterior sinal walls were absent; the orbital plate was perforated, and the bone showed evidence of osteitis. The sinus was blocked by a soft, friable and easily bleeding gray mass. The histologic observations are described in detail and illustrated by excellent photomicrographs. The rapid and destructive course of the lesion suggested malignancy, although there was no cachexia, pain or metastasis. Syphilis was excluded by a negative Wassermann reaction. The contrast between the clinical course and the histologic picture was striking. The latter represents fibrous osteitis with myeloplasts, the morphologic particulars consisting of globular or trabecular hyalinocalcareous formations. The complex question of the relation between inflammatory and blastomatous new formations of the bone is still obscure.

DENNIS, San Diego, Calif. [ARCH. OTOLARYNG.]

THE OXIDE-REDUCING POWER OF THE TONSILLAR TISSUES. F. VENTURA-GREGORINA, Arch. ital. di otol. **51**:437 (Sept.) 1939.

Using the method of Birch, Harris and Ray (2, 6-dichlorophenolindophenol), Ventura-Gregorina studied the oxide-reducing power of tonsillar and adenoid tissue removed from 40 patients, varying in age from 3 to 38 years. Especially considered was the relation of reduction oxides to the age of the patient and to the histopathologic structure of the tonsillar tissue. The results of the investigation indicate that when lymphatic hypertrophy is greater the oxide reduction is of higher value. In children up to the fourteenth year there is a greater degree of lymphatic hypertrophy than in adults and a larger extent of germinative centers, accompanied by a smaller quantity of stromal tissue. It also appears from the research that in the hypertrophic, chronically inflamed and hyperplastic tonsils, the important biologic phenomena of tissular respiratory activity progressively diminishes in relation to various complex factors, including, particularly, biochemical influences.

DENNIS, San Diego, Calif. [ARCH. OTOLARYNG.]

Diseases of the Lungs, Pleura and Mediastinum

BRONCHIECTASIS: A STUDY OF PROGNOSIS BASED ON A FOLLOW-UP OF 400 PATIENTS. KENNETH M. A. PERRY and DONALD S. KING, Am. Rev. Tuberc. **41**:531 (May) 1940.

The recent advances in the surgical treatment of bronchiectasis have suggested a wider application of this form of treatment for this condition. This study of the natural course of the disease was made in order to decide whether and in what circumstances a patient should be advised to submit to lobectomy, with its 10 per cent or less of operative risk.

A careful follow-up of 400 patients disclosed that the disease had its onset in the first two decades of life in 69 per cent of all cases, in 42 per cent in the first and in 27 per cent in the second decade. This is interesting from the standpoint of etiology, since the onset of the disease is usually associated with such acute infections of the respiratory tract as are especially common in early life. Bronchiectasis is the result of the superimposing of an infection on a mechanical deformity, obstruction and dilatation, of the bronchi. Clinical and experimental observations have confirmed the view that the abnormal forces created by collapse of the lung are those most likely to cause dilatation of the bronchi. The fre-

quency with which collapse occurs as a result of pneumonia, whooping cough, measles, etc. probably accounts for the high percentage of onset during the first two decades of life. Bronchiectasis does not result immediately on the development of the mechanical factors, since these conditions may lie dormant for many years, until purulent bronchitis is superimposed. The relation of sinusitis to bronchiectasis has been widely discussed, but the authors are of the opinion that there is no causal relation between the two conditions.

Dilatation of the bronchi alone does not give rise to symptoms (except hemoptysis) until infection occurs. Following infection, cough and purulent sputum occur, and hemorrhage in varying amounts is of frequent occurrence. Hemorrhage developed in 148 of the patients studied; it was sufficient to cause death in 4 cases.

The most frequent complications were recurring attacks of apical pneumonia; less often there are observed pulmonary abscess, abscess of the brain, failure of the right side of the heart, empyema and pyopneumothorax.

A twelve year study of this group showed the mortality among the conservatively treated patients to be 26 per cent. The operative mortality from 122 lobectomies of the modern type in 116 cases was 3.3 per cent. From these observations it appears that lobectomy is the treatment of choice for bronchiectasis, especially for the unilateral condition.

EUGENE H. SMITH, Ogden, Utah.

PNEUMONIA IN INFANTS AND CHILDREN. B. W. CAREY and T. B. COOLEY, J. Pediat. **15**:613 (Nov.) 1939.

A study of 630 infants and children with pneumonia is reported. Of these patients, 248 were treated with sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine), 106 were treated with specific antipneumococcus rabbit serum and 276 served as controls. Specific treatment with both sulfapyridine and serum apparently reduced the total duration of the pneumonia and the fatality rate. Specific treatment also lowered the percentage of complications of pneumococcic pneumonia, such as meningitis, mastoiditis and suppurative otitis media. The optimal blood concentration of free sulfapyridine is recommended as 4 mg. per hundred cubic centimeters or above. Evidence from this study suggests that sulfapyridine is as effective as sulfanilamide in the treatment of streptococcic pneumonia. Sulfapyridine had no beneficial effect on staphylococcic pneumonia in this group. Sulfapyridine was equally effective in treating pneumonia caused by any of the 32 types of Pneumococcus. The available specific serums for the different types were equally effective except for 2 cases of pneumonia caused by type XVIII pneumococcus, which may not have been a true type XVIII but a closely related unnumbered type above XXXII.

RAUH, Cincinnati.

LOCALIZED BULLOUS EMPHYSEMA ASSOCIATED WITH PNEUMONIA IN CHILDREN. B. BENJAMIN and A. E. CHILDE, J. Pediat. **15**:621 (Nov.) 1939.

A series of cases of localized bullous emphysema associated with pneumonia is reported. The characteristic roentgenologic appearance of this condition consists of one or more abnormal areas of diminished density, surrounded by thin, dense, smooth margins. These areas are spheroid or ovoid and sometimes loculated. They are easily seen when the surrounding lung tissue is comparatively clear; they may be merely suspected when infiltration is present in the contiguous lung tissue and become more definite as the lung becomes clearer. Their location is usually subpleural or intrapleural. As a rule, they contain only a small amount of fluid. The size varies from very small to balloonlike spaces occupying a large portion of one lung. These areas of bullous emphysema usually disappear in a few weeks, but occasionally some months may elapse before the roentgen appearance returns to normal. This condition is not accompanied by abnormal signs or symptoms unless enormous inflation results or the pleura ruptures with formation of a pneumothorax. Careful observation for a short period will differentiate this

condition from pulmonary abscess, localized pneumothorax, congenital pulmonary air cyst and diaphragmatic hernia. No treatment is necessary unless complicating conditions ensue.

RAUH, Cincinnati.

RESULTS OF TYPING PNEUMOCOCCI FROM SPUTUM IN FOUR HUNDRED AND FIFTY CASES OF PNEUMONIA AMONG INFANTS AND CHILDREN. W. J. AUGER, J. Pediat. **15**:646 (Nov.) 1939.

The sputum of 450 infants and children with pneumonia (obtained by suction) was typed and cultured. Pneumococci were present in the sputum of 83.3 per cent of the children. In children over 2 years the most common types were I, II, XIX, XIV and XVIII, and in children under 2 years, XIX, XIV and untypable pneumococci. Of the patients with type I pneumonia in an early stage who received no specific treatment, empyema developed in 20 per cent. Empyema developed in 16 per cent of those who had serum therapy and in only 8 per cent of those given sulfapyridine (2-paraaminobenzenesulfonamido]-pyridine). It was found that the mortality rate was very high for infants under 1 year, especially when the pneumonia was due either to the pneumococcus plus another pathogen or to an organism other than the pneumococcus. Staphylococcus aureus was a cause of death in 58.3 per cent of the infants under 1 year of age whose pneumonia was due to an organism other than Pneumococcus.

RAUH, Cincinnati.

INFLUENCE OF SPECIFIC SERUM ON PLASMA LIPIDS IN PNEUMONIA. A. V. STOESSER, Proc. Soc. Exper. Biol. & Med. **43**:168 (Jan.) 1940.

Stoesser has thoroughly studied the changes that occur in the plasma lipids during acute infections in children. This paper deals with the changes that occur when the patient receives a specific serum for pneumonia. Three subjects with similar attacks of pneumonia were chosen. It was found that the cholesterol values were already subnormal before the specific serum was administered. The response to the single dose of serum was a drop in the temperature in each instance to normal within twelve to twenty-four hours, and one day later, when the second blood sample was collected, the total cholesterol and esters had already returned to the normal range. After the fourth day of convalescence, all cholesterol values were normal and the roentgenograms showed complete resolution of the pneumonia.

The total fatty acids and the phospholipids were slightly depressed before the administration of serum. Immediately following the fall in temperature, there was a rapid increase in the total fatty acids and the phospholipid fatty acids while the phospholipids rose more slowly. The iodine numbers of the total fatty acids and of the phospholipid fatty acids underwent very little change, for the prompt response to serum therapy apparently prevented any marked drop. The intensity of the fat metabolism during pneumonia and the presence of bacterial toxins may be responsible for the fall in the plasma lipids to abnormal levels. The early use of a specific serum tends to control this alteration in lipid metabolism which is present in acute infections, such as pneumonia.

AUTHOR'S SUMMARY. [HANSEN, Minneapolis]

INFLUENCE OF SULFAPYRIDINE THERAPY ON PLASMA LIPIDS IN PNEUMONIA. A. V. STOESSER, Proc. Soc. Exper. Biol. & Med. **43**:201 (Jan.) 1940.

Specific serum therapy is able to prevent the rather marked changes in the serum lipids which occur in pneumonia. The introduction of chemotherapy brings up the question of its influence on the plasma lipids. This paper includes a study of 5 children with pneumonia who received sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine). The total cholesterol and esters were significantly lower than normal on the day the sulfapyridine was started. The response to this form of therapy was clinically satisfactory. After one day of no fever, the second blood sample was obtained, and the cholesterol values were found to have changed very little. On the fourth day of convalescence, when the third sample of blood was

collected there was some indication of a slight rise in the cholesterol. Following this, the pneumonic process began to resolve rapidly, and on the seventh day of convalescence the lungs were clear. The total cholesterol and esters had then returned to the normal levels.

The total fatty acid and phospholipid values were lower than the average figure during the period of the illness before the administration of sulfapyridine. Although the introduction of drug therapy was followed by a good clinical response, the total fatty acids were slow in rising to higher levels. There was a slight rise and then another drop in the phospholipids, and recovery from the low levels was retarded. The iodine numbers of the total fatty acids and phospholipid fatty acids were not markedly depressed during the height of the disease. They apparently had little time to fall to the low levels observed during the last stages of the febrile period when the disease is allowed to take its natural course.

FROM THE AUTHOR'S SUMMARY.

LOEFFLER'S SYNDROME—PLEUROPNEUMONIC EOSINOPHILIA. C. SANTOS, Rev. méd. latino-am. **25**:508 (Feb.) 1940.

Pleuropneumonia associated with eosinophilia is a benign condition, the chief importance of which is that it must be differentiated clinically from tuberculosis. The symptoms are fatigue, headache, lumbar or dorsal pain and mucopurulent expectoration. There are also pulmonary dulness, diminution of breath sounds and eosinophilia running as high as 70 per cent. The clinical course may run five to eight days or occasionally three to four weeks. The condition is probably an allergic phenomenon; tubercle bacilli are not found in the sputum, although Loeffler found a positive tuberculin reaction in 72 per cent of 51 cases. The author reports 3 cases from Brazil; the disease had formerly been reported from Portugal, Germany, France and Shanghai, China.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

ACUTE GINGIVOSTOMATITIS IN CHILDREN. J. D. MCKINNEY, Illinois M. J. **77**:269 (March) 1940.

Acute gingivostomatitis is a definite disease entity, occurring in a definite age group. Attempts to state its cause have caused considerable controversy. Its infectious character has not been proved. The rapid course of the disease is against any theory that the cause is a deficiency. There seems to be a seasonal appearance of the disease. It's course follows a rather definite pattern, and complications or sequelae are rare. Treatments of various types have been described, but none have proved to have specific value.

BARBOUR, Peoria, Ill.

METABOLISM IN IDIOPATHIC STEATORRHEA: I. THE INFLUENCE OF DIETARY AND OTHER FACTORS ON LIPID AND MINERAL BALANCE. S. H. BASSETT, E. H. KEUTMANN, H. VAN ZILE HYDE, H. E. VAN ALSTINE and E. RUSS, J. Clin. Investigation **18**:101 (Jan.) 1939.

Case histories and metabolic studies on 4 patients with idiopathic steatorrhea (3 adults, 1 youth aged 14 years) are presented. While these subjects exhibited great individual variation in tolerance of fat, the fecal excretion of fat in each was nearly constant for a given regimen. A very low dietary fat intake prevented steatorrhea. In 1 patient the tolerance of fat was not improved by replacing dietary starch with monosaccharide; in another patient a low starch diet seemed to prevent diarrhea and increase the ability to absorb fat. Sodium glycerophosphate and ox bile made the steatorrhea of 1 patient worse. An alkaline phosphate, a calcium salt or both caused an increase in the total amount of split fat in the feces. A reduction in the intake of calcium facilitated the absorption of fatty acids. This procedure resulted in loss of calcium and phosphorus from the body

in a subject with mild steatorrhea. Increase in dietary fat, when accompanied by steatorrhea, increased the loss of calcium in the feces at the expense of calcium stored in the body. Moderately high calcium and phosphorus intake in the absence of vitamin D failed to produce consistently positive balances of these elements.

GUEST, Cincinnati.

METABOLISM IN IDIOPATHIC STEATORRHEA: II. EFFECT OF LIVER EXTRACT AND VITAMIN D ON CALCIUM, PHOSPHORUS, NITROGEN, AND LIPID BALANCES. S. H. BASSETT, E. H. KEUTMANN, H. VAN ZILE HYDE and H. E. VAN ALSTINE, J. Clin. Investigation **18**:121 (Jan.) 1939.

Prolonged intramuscular administration of liver extract to patients with idiopathic steatorrhea (nontropical sprue) failed to cause improvement in the absorption of fatty acids, calcium, phosphorus or nitrogen. Oral administration of large doses of vitamin D caused the following changes: (*a*) Increased excretion of phosphorus in the urine before there was evidence of improved absorption of calcium. (*b*) Increased absorption of calcium from the intestine. (*c*) Increased absorption of magnesium from the intestine. (*d*) Increased absorption of phosphorus from the intestine. The magnitude of this increase was such that it was probably not entirely secondary to improved absorption of calcium and magnesium. (*e*) Some improvement in the absorption of fatty acid in 2 patients. This was interpreted as caused by improvement in the absorption of calcium or by decrease in its rate of propulsion through the small intestine, and probably not to improvement of the primary disorder. (*f*) Improvement of the absorption of water and nitrogen from the feces. These likewise were interpreted as secondary effects. GUEST, Cincinnati.

ACUTE APPENDICITIS (UNRUPTURED) OCCURRING IN YEAR OLD INFANT. H. J. MORRISON and L. LEE, J. M. A. Georgia **29**:202 (March) 1940.

The case is reported in detail. The unusual features were (1) the infant continued to eat and relish food after the onset of symptoms and (2) was able to rest (sleep) at long intervals without sedatives. FROM THE AUTHORS' SUMMARY.

GLYCOGEN DISEASE. S. VAN CREVELD, Medicine **18**:1 (Feb.) 1939.

Van Creveld summarizes the clinicochemical observations in 2 cases of glycogen disease:

1. A combination of hypoglycemia and ketosis in the fasting condition
2. An abnormal epinephrine effect
3. An abnormal curve in the dextrose tolerance test
4. Normal tolerance for galactose and fructose
5. Absence of the so-called initial insulin hyperglycemia
6. Normal values for the diastase activity of the blood and urine and a normal diastase activating effect of the serum
7. Increased glycogen content of the blood, which could not be explained by leukocytosis
8. Normal glycogen-splitting activity of the blood serum
9. Decreased lysis of the blood glycogen in incubation for two days at 37 C., compared with controls
10. Normal protein partition of the blood plasma, especially of globulin
11. Hypercholesteremia; also marked sensitivity to insulin, probably due partly to the initial hypoglycemia

Physically, patients often show small extremities, sometimes associated with edema of the face. Infantilism is the rule.

There is a familial tendency. There has been a family history of diabetes in a few cases, and 1 patient with glycogen disease later became diabetic.

Cardiomegalia glycogenica frequently occurs alone but may occur in association with glycogen disease of other organs, e. g., the tongue or the skeletal muscles. It is suggested as a cause of "idiopathic ventricular hypertrophy" and may be identified with diffuse rhabdomyomatous hypertrophy.

The author discusses the differentiation of glycogenic hepatomegaly from cirrhosis of the liver, congenital fatty liver, the reticuloendotheliosis group (Gaucher's disease and Niemann-Pick disease) and the hepatomegaly of treated diabetes. There are similarities between the latter condition and glycogenic hepatomegaly.

The genesis of glycogen disease is still poorly understood, but the author concludes that the disease is probably endocrine in origin and that it may be associated particularly with dyspituitarism.

As to prognosis, some observers believe there is a predisposition to infections, but the author does not believe this to be the case. Both of his patients showed some clinical improvement at about puberty. The Parnas and Wagner patient became diabetic at the age of 16. Other observers have reported improvement in their patients as the latter grew older.

Therapeutically, a high carbohydrate, low fat diet is helpful. Endocrine preparations which have been tried with variable results are: thyroid, pituitary, gonadotropic substances, epinephrine. Choline apparently acted favorably on the ketosis in the author's cases. Linneweh observed a decrease in the size of the abdomen with the use of a cholic acid–lecithin compound. Roentgen therapy is of questionable value.

An extensive bibliography is appended. LIMPER, Louisville, Ky.

THE SECRETIN TEST OF PANCREATIC FUNCTION. H. LAGERLÖF, Quart. J. Med. **8**:115 (April) 1939.

Lagerlöf concluded that two requirements for a functional test of external pancreatic secretion had been fulfilled: (1) a pure secretin preparation and (2) a clinical procedure by which the duodenal juice could be quantitatively recovered without admixture of gastric secretion. The author stated that the first requirement had been met by the work of Hammarsten and others and that the second requirement was met by the use of a special double tube for the stomach and duodenum.

Lagerlöf reported studies on the normal function of the pancreas, normal variability and certain pathologic deviations. BRADFORD, Rochester, N. Y.

THE CAUSATION OF THE LOW BLOOD SUGAR CURVE IN COELIAC DISEASE. T. CRAWFORD, Quart. J. Med. **8**:251 (July) 1939.

Crawford carried out intravenous dextrose tolerance tests on 12 patients with celiac disease, 11 of whom showed typically low blood sugar curves after oral administration of the sugar.

No significant differences were found between the intravenous tolerance curves of patients with celiac disease and normal persons. Insulin sensitivity tests in 6 of the patients were closely similar to those in normal subjects.

From these results the author concludes that no abnormality of intermediate carbohydrate metabolism exists in patients with celiac disease and that the low blood sugar curve of the disease is due to a delay or a defect in the absorption of carbohydrate from the bowel. BRADFORD, Rochester, N. Y.

PROGNOSIS IN COELIAC DISEASE. C. HARDWICK, Arch. Dis. Childhood **14**:279 (Dec.) 1939.

Seventy-three hospital cases of celiac diseases were studied between 1925 and 1938, and all but 14 per cent of the living patients have been traced. Twenty-six patients died. Death was usually due to an exacerbation of the disease, the diarrhea increasing and dehydration and intoxication becoming marked. Only 4

children died from bronchopneumonia. Seventeen patients appeared to have recovered clinically and biochemically for more than three years; 10 had been in a similar condition for less than three years. Together these form a group of 37 per cent of the whole. Six patients are still in the first phase of activity of the disease. Four patients were thought to be well until stool analyses showed steatorrhea. These patients are in a quiescent phase of the disease, which, if it becomes reactivated in adult life, is usually diagnosed as idiopathic steatorrhea. To such the name "latent celiac disease" should be given. Patients who have had celiac disease tend to remain dwarfed, but their intellect is not affected and their teeth remain good. Anemia does not as a rule persist. KELLY, Milwaukee.

REPORT OF A CASE OF STRANGULATED UMBILICAL HERNIA. R. KOHAN and C. URRUTIA, Rev. chilena de pediat. **10**:273 (May) 1939.

The authors report this rare condition in an infant less than 1 month old. A large mass of intestine and omentum was contained in the hernial sac. Strangulation of the mass had ensued. Operation was attempted but was unsuccessful, and the case terminated fatally. SCHLUTZ, Chicago.

PSYCHOGENIC VOMITING. AMPARA and M. ARCAYA V., Rev. chilena de pediat. **10**:345 (June) 1939.

There are many psychogenic influences in cases of psychogenic vomiting. The only child, the child in an adult environment, the child in a maladjusted environment are frequently victims of this disorder.

Fifty children with severe vomiting are reported on. The age varied between 5 and 10 years. The intelligence quotients of 38 of the subjects were normal or above normal. The authors recommend psychiatric treatment as the most effective procedure for this type of patient. SCHLUTZ, Chicago.

PERFORATION OF THE GALLBLADDER IN CHILDREN. C. S. HUANG, Chinese M. J. **56**:564 (Dec.) 1939.

This review of the literature and report of a case comes from the department of surgery of the National Medical College of Shanghai, China. The author had found 22 similar cases in the literature. All of the patients were children. In nearly all of them the perforation accompanied or followed typhoid fever, which was undoubtedly the factor in the author's case, as the patient's serum showed agglutination in the high dilution of 1:5,120. In adults a calculus is nearly always the cause of perforation. A calculus was present in only one of the children whose cases were reviewed.

The author's patient was a 9 year old Chinese girl. She became entirely well thirty-five days after the operation, which is in contrast to the usually high mortality. The reduction in mortality is best attacked by preventing perforation: When cholecystitis complicates scarlet fever and does not respond to conservative treatment, the surgeon should not hesitate to perform surgical drainage of the gallbladder. NEFF, Kansas City, Mo.

Nervous Diseases

ABSCESS OF THE BRAIN: RELATION OF THE HISTOLOGIC TO THE CLINICAL FEATURES. BERNARD J. ALPERS, Arch. Otolaryng. **29**:199 (Feb.) 1939.

The author presents 27 cases of abscesses of the brain in which the histologic structure is described with special reference given to encapsulation and its optimum formation time, stated here to be from three to four weeks. The time element, the type of organism present and the resistance of the host are the three paramount factors in the development of the capsule. GREENWOOD, Chicago.

RECOVERY FROM HEMOLYTIC STREPTOCOCCIC MENINGITIS OF OTITIC ORIGIN. S. S. GONNE, M. W. MICHELS and T. WATSON, Arch. Otolaryng. **29**:382 (Feb.) 1939.

The case is presented of a 9 year old girl in whom purulent otitis media had been present for five years prior to the appearance of meningeal symptoms. Prompt subsidence of symptoms and clinical findings, with no complications other than transient cyanosis, followed sulfanilamide therapy. GREENWOOD, Chicago.

HEREDITARY CHOREA: ST. ANTHONY'S DANCE AND WITCHCRAFT IN COLONIAL CONNECTICUT. P. R. VESSIE, J. Connecticut M. Soc. **3**:596 (Nov.) 1939.

A family group, which emigrated from Bures, in East Anglia, England, to the Watertown Plantation in Massachusetts in 1630, has now a hereditary family tree of twelve generations. Huntington, after whom the hereditary type of chorea is named, published his paper in 1872, but the original description has to be credited to C. O. Waters, who noticed the characteristic features (chronicity, progressiveness, hereditary quality, occurrence in adults, dementia) as early as 1841. A gruesome chapter of witch trials and burnings in the New England states is connected with the history of this disease. The Long Islanders called it "St. Anthony's dance"—not to be confused with "St. Anthony's fire"—while an old English dialect names it "magrums," meaning "mad staggers and fidgets."

This type of chorea is a mendelian dominant character; it does not skip a generation and is not sex linked. The disease will develop in about 50 per cent of the offspring of a parent who is afflicted by it. ROSENTHAL, St. Paul.

THE BEHAVIOR EXAMINATION OF INFANTS AS AN AID TO EARLY DIAGNOSIS OF CENTRAL NERVOUS SYSTEM DISEASE. HELEN THOMPSON and PHILIP A. BEARG, J. Pediat. **16**:570 (May) 1940.

Two infants were referred for psychologic study because of feeding difficulty. In both instances the study indicated abnormality of the central nervous system not suggested by either the pediatric or the neurologic examination. In the first case psychologic examination at 28 weeks of age revealed atypical behavior. Subsequent encephalographic examination revealed cortical atrophy. The second child presented an irregular atypical behavior pattern at 25 weeks. Encephalographic examination suggested congenital developmental defects of the central nervous system. At the age of 4 years both children gave evidence of definite retardation. The authors stress the importance of early psychologic examination.

RAUH, Cincinnati.

FRIEDREICH'S ATAXIA ASSOCIATED WITH DIABETES MELLITIS. N. S. SCHLEZINGER and KURT GOLDSTEIN, New York State J. Med. **40**:415 (March 15) 1940.

The cases are reported of 2 sisters aged 13 years and 22 years, respectively. Both had diabetes during the course of Friedreich's ataxia. They gave evidence of endocrine dysfunction in the form of hypopituitarism, hypothyroidism and hypogonadism. Eighteen similar cases have been reported in literature.

AIKMAN, Rochester, N. Y.

PNEUMOCOCCAL MENINGITIS TREATED SUCCESSFULLY. SILVIO VUKOV, Northwest Med. **39**:221 (June) 1940.

A case of pneumococcic meningitis in a 5 year old boy is reported. Type XI pneumococcus was demonstrated on culture four days after admission of the child to the hospital. He had been given sulfanilamide, an anti-influenzal serum and transfusions. He was then given sulfapyridine and specific antiserum. Administration of the antiserum was repeated on the third day because of a relapse. He was discharged as well after eighteen days in the hospital.

ROBERTSON, Omaha.

PARKINSONISM: AN ACCOUNT OF THE DISORDER AND ITS TREATMENT, WITH SPECIAL REFERENCE TO HIGH ATROPINE DOSAGE THERAPY. J. F. HUGHES, M. J. Australia **2**:174 (Aug. 24) 1940.

Hughes reviews the various methods of treatment of parkinsonism. In his own experience the best results, both mental and physical, in the treatment of the post-encephalitic form are obtained with a high dosage of atropine. To adults approximately ⅓ grain (0.02 Gm.) per day is given.

GONCE, Madison, Wis.

JAW WINKING. P. G. DOYNE, Proc. Roy. Soc. Med. **33**:514 (June) 1940.

The case of a child 2½ years of age is reported. It was noticed at birth that the left upper eyelid opened widely when the child ate and fell when the mouth closed. Her teeth were devoid of enamel. Her mother and father had a similar condition. Eighteen members in three generations of the patient's family were affected.

WILLIAMSON, New Orleans.

A CASE OF BENIGN LYMPHOCYTIC MENINGITIS OCCURRING DURING OTITIS MEDIA. T. MARCULESCU and V. LASCU, Bull. Soc. de pédiat. de Iasi **10**:5, 1939.

The authors report an example of two distinct maladies occurring coincidentally in the same person. The precipitating factor was probably prolonged exposure to cold.

LESLIE, Evanston, Ill.

ACUTE ASEPTIC PURULENT MENINGITIS IN AN INFANT. P. NOBÉCOURT, Presse méd. **48**:15 (Jan. 3-6) 1940.

A baby of 5 months began to cough and was treated for bronchitis. The following day he was extremely fretful and refused the breast. He was admitted to the hospital, where he was found to have a temperature of 101.4 F. and an infection of the respiratory tract. The next evening his temperature rose to 105.8 F.; he was drowsy and dyspneic, and moist rales increased in number in his chest. Mild diarrhea appeared. On the fifth day his temperature was lower, but he was extremely lethargic. His neck was slightly stiff, but the Kernig sign was bilaterally negative. Purulent fluid was obtained by lumbar puncture, with no organisms present. The cells were nearly all polymorphonuclears which did not turn blue with vital staining. Recovery occurred with no specific treatment. Further lumbar punctures showed gradual reduction of the cell count, with lymphocytes replacing the polymorphonuclears.

Nobécourt presents the case as a typical example of acute aseptic purulent meningitis. He discusses the differential diagnosis, eliminating acute lymphocytic meningitis and acute serous meningitis.

DAFFINEE, Boston.

ACUTE SEROUS MENINGITIS. P. NOBÉCOURT, Presse méd. **48**:374 (April 10-13) 1940.

Nobécourt presents a case of acute serous meningitis in a boy of 13 years, which typefies the usual course of this disease. The onset is sudden, with fever, headache, vomiting and abdominal pain. Convulsions or coma may be seen. Within a few hours meningitic symptoms appear. Stiffness of the neck is one of the earliest signs and is the last to disappear. Kernig's sign is generally absent. Lumbar puncture shows a clear fluid under slightly increased pressure. The cells in the cerebrospinal fluid are increased moderately, with polymorphonuclear forms predominating. The protein content of the fluid is slightly increased. No organisms can be discovered. The blood shows slight leukocytosis. The disease runs its course in six to ten days, with the temperature dropping by lysis. Recovery is complete, with no sequelae.

DAFFINEE, Boston.

FURTHER EVALUATION OF THE ACTION OF SULFANILAMIDE IN MENINGOCOCCUS MENINGITIS. A. LEONE, Med. inf., Rome **11**:57 (March) 1940.

Leone in 1938 reported on the results of treating meningococcus infection in 18 with sulfanilamide products. He now increases his case reports to 43.

Of the 25 new patients, 7 died and 2 have hydrocephalus, 1 of the latter being deaf. For 11 the sulfanilamide treatment was associated with serum therapy; 4 of these died, 1 of bronchopneumonia after the spinal fluid had become sterile. Of the other 14, 3 died of bronchopneumonia, 2 after the spinal fluid had become sterile.

Sterilization of the spinal fluid occurred between the tenth and the twenty-second day when serum also was given and between the fourth and the fourteenth day when sulfanilamide alone was given.

The sulfanilamide was given not only by mouth but intravenously.

HIGGINS, Boston.

PURULENT MENINGITIS FROM PFEIFFER'S BACILLUS AND FRANKEL'S PNEUMOCOCCUS WITH RECOVERY. IRENE VERROTTI, Med. inf., Rome **11**:89 (April) 1940.

The patient was a 10 month old breast-fed girl who at 5 months of age had staphylococcus meningitis; recovery bacteriologically was complete, but residual hydrocephalus required weekly ventricular punctures. The circumference of the head was 47.5 cm. The onset of the present condition was with an infection of the upper respiratory tract and fever; five days later the fontanel bulged and ventricular puncture revealed a greenish yellow, purulent fluid with both pneumococcic and influenzal bacilli. Treatment was by sulfapyridine, 5 Gm. per day. Two days later the ventricular fluid was sterile and clinical improvement apparent. Six months later the child had had no recurrence of the meningitis.

HIGGINS, Boston.

INFLUENZAL MENINGITIS TREATED WITH SULFANILAMIDE. Y. BESEDOVSKY, Rev. Soc. pediat. de Rosario **4**:183, 1939.

The author, after stating that in the literature he reviewed he found only 1 case of recovery from meningitis due to Pfeiffer's bacillus, records a case in which the spinal fluid was apparently sterilized by intramuscular and intrathecal sulfanilamide. Treatment was interrupted, and several months later the child succumbed to influenzal meningitis. The author stresses the fact that although the spinal fluid may be sterile there may be viable influenza bacilli in the central nervous system.

DIETRICH, Beverly Hills, Calif.

SPASMOPHILIA IN INFANTS. G. BRAKHAGE, Med. Klin. **36**:156 (Feb. 9) 1940.

The article consists of a review of the subject.

SIEMSEN, Chicago.

TREATMENT OF LITTLE'S DISEASE WITH THE BULGARIAN CURE. H. STIEDA, Med. Klin. **36**:191 (Feb. 16) 1940.

Spastic patients with mental deficiency showed no response to belladonna. Four of 5 patients with normal intelligence (in whose cases the author presumes a possible encephalitic cause) showed definite improvement manifested by better tolerance of massage and exercises, which caused practically no pain, and by greater relaxation of muscle spasms.

SIEMSEN, Chicago.

SYMPATHICOBLASTOMA. C. HOOFT, Maandschr. v. kindergeneesk. **9**:99 (Dec.) 1939.

Hooft presents a description of 3 cases of sympathicoblastoma of the Hutchinson type in 2 girls aged respectively 21 months and 5 years, and in 1 boy, aged 2⅓ years. All 3 children showed the classic symptoms, though the first one also had

some other disturbances. The author stresses the diagnostic significance of sternal puncture in such cases. In all 3 cases the material obtained showed the sympathicoblasts described for the first time in 1938 by Kato and Wachter.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of the Genitourinary Tract

CHRONIC PYELONEPHRITIS—A CAUSE OF HYPERTENSION AND RENAL INSUFFICIENCY. WILLIAM S. MCCANN, New York State J. Med. **40**:400 (March 15) 1940.

Cases are reported to show the relation between mild urinary infections and later hypertension and renal insufficiency. The patients were adults. The effects were especially serious in their relation to the toxemias of pregnancy. Even mild pyelonephritis requires more careful general study. The seriousness of obstructive lesions is stressed.

AIKMAN, Rochester, N. Y.

PERINEPHRITIS. I. J. WEYMAN, M. J. Australia **2**:152 (Aug. 17) 1940.

Nonsuppurative perinephritis is an independent nosologic entity, generally characterized by lumbar, lumboabdominal or sacral pain. This is particularly localized in special points, which correspond either with the kidney and the ureter or with the course of the nerves related to, or in contact with, the kidney. The painful symptoms may be accompanied with hematuria of varying intensity. The diagnosis of perinephritis can be formulated only after careful clinical, urologic and roentgen investigation, to the exclusion of all other forms of renal disease. As the disease is noticeably more frequent on the right side than on the left, it follows that an abdominal lesion on the right side requires careful evaluation for possible errors in the interpretation of pain, especially when the urine is normal. The most rational treatment, in appropriate cases, is decapsulation of the kidney, extirpation of the whole of the perirenal fat and temporary fixation of the kidney until adhesions have formed, with two or three points of support.

GONCE, Madison, Wis.

PATHOLOGIC CHANGES OF THE HYPOPHYSIS IN RENAL DISEASE. B. P. KUCHERENKO, Vrach. delo **22**:31 (Jan.) 1940.

The author reports his observations on the postmortem histologic changes of the hypophysis in a group of 25 persons with renal disease as compared with a control group of 120 persons all between 16 and 60 years of age. The group of subjects with renal disease included persons with nephritis, nephrosis, amyloidosis, nephrosclerosis and carcinoma, while the control group comprised 25 who had died accidentally, the rest consisting of a miscellaneous group with diseases other than renal. A special method of preparation and staining of the material was used in the histologic study of all the portions of the hypophysis and is described by the author in detail.

The author's results indicate that the most characteristic changes of the hypophysis in renal disease are the increase in the basophilic and neutrophilic intravascular colloidal content and the concomitant increase in the basophilic cellular element of the anterior lobe.

BODER, Los Angeles.

ROENTGEN DIAGNOSIS OF MALIGNANT RENAL NEOPLASMS. M. M. WEISFLIGEL, Vrach. delo **22**:41 (Jan.) 1940.

The author presents a discussion of the diagnosis of malignant renal neoplasms from clinical, laboratory and roentgen standpoints, with 10 case reports. The conclusions are as follows:

1. In a great majority of cases it is possible to establish clinical (antemortem) diagnosis of renal tumors.

2. Roentgen examination is of the greatest value of all known clinical diagnostic procedures, but it aids the clinician only if used correctly and systematically.

3. The most satisfactory results are obtained by the systematic application of the following four methods: (*a*) roentgenographic study of the chest and abdomen; (*b*) dilation of the large intestine by introduction of air; (*c*) pyelographic study, and (*d*) gastrointestinal study. Roentgen examination of the skeleton is of value in the presence of metastasis.

4. Pyelographic study is of decisive value in the diagnosis of renal tumors. The author prefers retrograde pyelography, for he believes, like many other investigators, that it is of greater value than the intravenous method in the diagnosis of malignant renal growths.

5. The correct use of the aforementioned roentgen procedures may enable one to establish the correct diagnosis even without the application of pyelography.

BODER, Los Angeles.

PSEUDOHERMAPHRODITISM AND GIGANTISM WITH PRECOCITY. J. MUNK, Maandschr. v. kindergeneesk. **9**:269 (April) 1940.

In the urine of a child 5 years old with gigantism and pseudohermaphroditism were found a considerable number of estrogenic units and of male (comb growth) units. Similar quantities were found in the urine of a boy, also 5 years old, with virilism and gigantism (adrenogenital syndrome). In neither case were symptoms present, which speaks in favor of a cerebral or adrenal tumor.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of the Ductless Glands; Endocrinology

HYPERTROPHY AND HYPERPLASIA OF ISLANDS OF LANGERHANS IN INFANTS BORN OF DIABETIC MOTHERS. E. B. HELWIG, Arch. Int. Med. **65**:221 (Feb.) 1940.

The pancreases of 9 infants of diabetic mothers and of 9 infants of nondiabetic mothers were studied. The islands of Langerhans in the infants of diabetic mothers exhibited a variable degree of hypertrophy and hyperplasia, most marked in those infants nearing full term when they were born. The nuclei were frequently enlarged and occasionally hyperchromatic. The stroma and to a less degree the islands frequently were infiltrated with eosinophilic granulocytes, many of which were mature. This infiltration was not present in the control group. One infant in the control group, whose mother was not known to have diabetes, showed hypertrophy and hyperplasia of the islands and no obvious anatomic cause of death. I am forced to conclude that some infants of diabetic mothers have definitely larger amounts of insular tissue than infants of nondiabetic mothers. This is particularly marked in those infants whose greater birth weights suggest a possible excess of growth stimulus. On the other hand, it must be recognized that a fair number of the pancreases of infants of diabetic mothers will fall in the normal range of insular size. The blood sugar levels on the whole show little correlation with insular size, the lowest level of blood sugar, 30 mg. per hundred cubic centimeters, occurring in an infant dying of subtentorial hemorrhage, and one of the higher values, 190 mg. per hundred cubic centimeters, occurring in a stillborn infant who had the largest islands of any in the series.

FROM AUTHOR'S SUMMARY. [ARCH. PATH.]

THE DIAGNOSTIC SIGNIFICANCE OF CRANIAL ROENTGENOGRAMS IN PITUITARY DISEASE. MAX A. GOLDZIEHER, Endocrinology **27**:185 (Aug.) 1940.

Five hundred cases of pituitary disease were studied to determine the diagnostic significance of structural abnormalities of the cranium. Cranial dysplasia was noted in 96 per cent, as compared with 9 per cent of a control series.

It is concluded that growth of the facial portion of the cranium and development of the paranasal sinuses and mastoid cells is inhibited in the "pituitary dwarf" and in cases of pituitary infantilism. Conversely, excessive expansion of the cancellous bone and of the sinuses is noted in cases of acromegaly, gigantism and other instances of overactivity of the anterior lobe such as obtains in eunuchoidism and in certain cases of precocious puberty or adiposogenital dystrophy of the tall variety.

Inadequate function of the anterior lobe during adult life yields a progressive diffuse sclerosis of the cranial bones which appears either in the previously normal cranium or is superimposed on an originally hypoplastic skull but is particularly marked in previously overexpanded cancellous bone tissue. These changes appear ten times more frequently in the female than in the male. JACOBSEN, Buffalo.

ENDOCRINES IN RELATION TO GROWTH IN CHILDHOOD. I. A. ABT, Illinois M. J. **77**:137 (Feb.) 1940.

Abt reviews some of the important points in the relation of hormones to bodily growth and development. The therapeutic value of a few of these hormonal remedies has been proved in the treatment of some clinical conditions in man. Treatment with other hormonal extracts is still in the experimental stage.

BARBOUR, Peoria, Ill.

EFFECT OF PITUITARY THYROTROPIC EXTRACT IN SUBJECTS WITH LOW BASAL METABOLIC RATES. E. P. SHARPEY-SCHAFER and I. SCHRIRE, Quart. J. Med. **8**:195 (July) 1939.

The pituitary thyrotropic extract used was obtained from pituitary anterior lobes of hogs. It contains some gonadotropic principle which the authors state cannot be removed without diminishing the thyrotropic activity of the substance. The effect of the material when injected intramuscularly was assessed by observation of (1) the clinical reaction, (2) the urinary excretion of creatine and (3) the basal metabolism.

Each of 22 normal subjects investigated responded to the injection of the thyrotropic extract. Five subjects with low basal metabolic rates reacted in a normal manner. Three subjects with myxedema and a cretin failed to respond.

Three subjects without evidence of thyroid deficiency but with low basal metabolic rates failed to respond to the injection of large doses of thyrotropic extract. In 1 case a biopsy of the thyroid showed no evidence of increased activity as a result of the injection. A patient with acromegaly also failed to respond.

BRADFORD, Rochester, N. Y.

THE DIFFERENTIAL DIAGNOSIS OF FORMS OF BASOPHILISM (CUSHING'S SYNDROME) PARTICULARLY BY THE ESTIMATION OF URINARY ANDROGENS. A. C. CROOKE and R. K. CALLOW, Quart. J. Med. **8**:233 (July) 1939.

The urinary excretion of androgenic substances was studied in 4 cases of basophilism.

In the case of a 25 year old man and that of a 6 year old girl, very high levels of excretion of 17 = ketosteroids were found. In each case, adrenal cortical tumors were present.

In the case of a girl aged 12 years and that of a woman aged 33 years, the excretion of androgenic substances was not significantly increased. In these cases, adrenal cortical tumors were absent.

The authors suggest that the determination of 17 = ketosteroids in the urine is a valuable test for the presence of adrenal cortical tumors in cases of basophilism.

BRADFORD, Rochester, N. Y.

PRECOCIOUS PUBERTY IN A BOY OF ONE YEAR. I. FRASER, Brit. J. Surg. **27**:521 (Jan.) 1940.

Fraser reports a case of extreme virilism in a boy of 12 months, presumably the youngest patient on record. Precocity in bone development and dentition was noted. The value of the capon and colorimetric tests, as well as of the ponceau-fuchsin stain, was demonstrated. The boy until the age of 6 months was normal. When the penis began to enlarge rapidly, the prostate became the size of a walnut, and erections were almost constant. Masturbation took place frequently, pubic hair appeared and the acne of puberty appeared on the face. The face became old for the age, the voice deep pitched, the hands greatly enlarged and muscular development excessive; the appearance of the epiphyses was greatly in advance of his age, and the body weight increased out of all proportions. He ate about three times the supply of food normally given a child of his age. Mentally, he was retarded. He was unable to talk and rarely used the "mamma-baba" words expected of a child of 12 months. He seemed to have little affection except for food. From the age of 6 months he lost his cleanly habits as regards urine and feces. He became bad tempered and difficult to manage. The author does not claim that these changes had any direct connection with his increased virilism. Briefly, the boy's age was (1) 12 months by calendar, (2) 12 months by mental advancement, (3) 5 years by bone epiphyses, (4) 3 years by dentition, and (5) 18 years by sexual organs (penis and prostate, but not testicles). Biologic tests carried out on the urine revealed that the boy at 12 months of age was more virile than the average man. Abdominal exploration revealed a tumor the size of a golf ball above the right kidney. The rest of the abdominal contents felt normal. After considerable delay, the second operation was performed when the boy was 18 months old. A high kidney incision was made. The twelfth rib was retracted and the adrenal tumor delivered with much greater ease and less bleeding than was expected. The tumor was pyriform, with the apex apparently attached without a stem to the inferior vena cava. The child was back in bed in thirty minutes; he recovered well and took fluids ravenously. Suddenly, twenty hours later, he collapsed and died. Complete necropsy was performed, but no abnormality other than enlargement of the vesicle and prostate could be found.

J. A. M. A.

THE USE OF ESTROGENS IN OBSTETRICS AND GYNECOLOGY. A. I. S. MACPHERSON, Edinburgh M. J. **47**:406 (June) 1940.

In the general consideration of this subject the author devotes a paragraph to vulvovaginitis before puberty. He states that estrogens have been replaced in the treatment of prepubertal vulvovaginitis by sulfonamides. However, estrogens are an adjuvant to chemotherapy or even a substitute if the sulfonamide is not well tolerated by the patient.

NEFF, Kansas City, Mo.

THE HYPOPHYSIS AND PANCREATIC INSULIN. H. P. MARKS and F. G. YOUNG, Lancet **1**:493 (March 16) 1940.

The daily administration of a crude extract of the anterior lobe to normal rats for two weeks led to a rise of the insulin content of the pancreas to nearly twice the normal value. The "insulin-increasing" or "pancreotropic" substance accompanies the diabetogenic and growth-promoting substances during ammonium sulfate fractionation of a crude extract, but it is not identical with either of these substances.

Extracts which are insulin increasing in the rat may either reduce the insulin content of the dog's pancreas to a low level or leave it without significant change, according to whether the extract is diabetogenic or not.

LANGMANN, New York.

Diseases of the Muscles, Bones, Joints and Lymph Glands

SKELETAL LIPOGRANULOMATOSIS. SAMUEL KLEINBERG, Bull. Hosp. Joint Diseases **1**:120 (Oct.) 1940.

A girl 15 years of age had had severe cramplike pains in the lower extremities for about 19 months, apparently initiated by forcefully striking the lower part of the back against a cement step. Contractures developed, with inability to stand or walk; two weeks before admission to the hospital she began to have pains in the crown of her head, and nine days later she became blind. The eyegrounds showed choked disks and hemorrhages into the retina. The blood pressure was elevated. Roentgenograms showed some thinning of the sacrum and of the fifth lumbar vertebra. The value for blood cholesterol was 260 mg. per hundred cubic centimeters. Tissue from a bulging mass in the left sacral region showed large vacuolated lipoid-containing cells. The diagnosis of skeletal lipogranulomatosis was made in spite of the absence of the classic picture of involvement of the skull with exophthalmos and diabetes insipidus.

Radium and roentgen treatments relieved the pain, and with the overcoming of the contractures the patient became fairly comfortable and able to walk. The original focus of xanthomatosis, however, increased in size. On the other hand, during three years no new recognizable foci have appeared.

LESLIE, Evanston, Ill.

A CASE OF MUSCULAR HEMANGIOMA. C. INFANTE and A. C. L. CUNEO, Rev. Soc. pediat. de Rosario **4**:192, 1939.

A hemangioma in the serratus posticus muscle of a 16 year old girl is reported. The asymptomatic progress and the tendency to produce phleboliths are stressed in the discussion. Disability and operative difficulties are entirely dependent on the particular muscle affected.

DIETRICH, Beverly Hills, Calif.

STILL'S DISEASE AND GOLD TREATMENT. H. HALBERTSMA, Maandschr. v. kindergeneesk. **9**:39 (July) 1940.

A girl 14 years old, who for two years had been suffering from high fever, exanthems and pain in the joints, all symptoms suggesting sepsis, reacted favorably to administration of high doses of salicylate. After extensive examination and exclusion of a number of other rare diseases, the diagnosis of Still's disease was accepted. When a first series of injections of a gold compound gave a remarkable decrease of the high sedimentation rate (though the clinical condition remained the same), these injections were repeated in stronger doses, with great amelioration of the condition. A third and a fourth "gold cure" in the course of two years resulted in complete recovery of the girl.

VAN CREVELD, Amsterdam, Netherlands.

FENESTRAE PARIETALES SYMMETRICAE. T. HALBERTSMA, Maandschr. v. kindergeneesk. **9**:89 (Dec.) 1939.

The author presents a description of a family of 17 persons, of whom 5 showed fenestrae parietales symmetricae, whereas 1 person had only slight depressions of the skull on the same places as the other members. No other congenital changes were observed. The older members of the family complained of vague headaches. In 1 of the grandchildren the development of the fenestrae could be studied; it appeared that one month after birth the openings became evident, as part of a cranial defect in the form of a T, of which the fenestrae formed the cross part. At the age of 1¾ years the fenestrae, which originally had been communicating, were separated into two separate ones by means of a small medial piece of bone. The fenestrae in the author's case thus arose in a way which differed from that noted in Zarfl's case (1935). The author prefers the name fenestrae to the term foramina parietalia permagna.

VAN CREVELD, Amsterdam, Netherlands.

A Case of Morquio's Disease. H. Broekema, Maandschr. v. kindergeneesk. **9**:240 (March) 1940.

A case of Morquio's disease in a 2½ year old boy is described. Laboratory examination revealed only a too high phosphatase content of the blood serum. The boy had atrophic disks and semialbinotic fundi. No other cases of the disease occurred in the family. The differential diagnosis is discussed briefly, as are the theories with regard to the possible cause of the condition. The gradual transition between the early slight condition and the pronounced one described by Morquio in 1928 is emphasized. van Creveld, Amsterdam, Netherlands.

A Case of Still's Disease (Rhonheimer Type) with Ocular Complications. T. Halbertsma and F. A. Melchior, Maandschr. v. kindergeneesk. **9**:405 (July) 1940.

A description is given of a case of chronic juvenile arthritis (Still's disease, Rhonheimer type) in a girl of 8 years, which was complicated by an ocular anomaly (chorioretinitis exudativa). The symptoms were as follows: 1. Multiple symmetric swelling of the knees, wrists, finger joints and cubital joints, which were very painful. 2. Swelling of regional lymph glands and muscular atrophy in the neighborhood of the affected joints, of which the first diminished but the second remained unaltered in the course of the disease. 3. An exudative inflammation at the background of each eye, stretching over almost the whole retina, probably originating from the underlying choroid, and notable dilatation of the conjunctival vessels with bluish discoloration of the scleras, with altering localization and of unknown origin. The differential diagnosis was made and the probable causes discussed. The frequency of association of ocular complications with this disease is discussed. van Creveld, Amsterdam, Netherlands.

Skin Diseases; Allergy

Erythema Infectiosum: Clinical Observations During an Epidemic. J. M. Rector, J. Pediat. **15**:540 (Oct.) 1939.

This is a report of 43 cases of erythema infectiosum seen during an epidemic in San Francisco during the spring and summer of 1938. The constitutional symptoms were slight. The salient feature of the disease was the rash, which usually made an initial appearance on the cheeks where it occurred as rose red maculopapules that rapidly coalesced into a confluent mass with a symmetric butterfly configuration. The nasolabial region was not involved, producing a circumoral pallor. Within twenty-four to thirty-six hours the rash developed on the trunk and extremities. On the trunk it appeared as a fine discrete maculopapular eruption, practically indistinguishable from German measles. On the extremities the rash was more marked on the extensor surfaces, where it occurred as large macules or maculopapules that assumed a violaceous tinge. These faded from the center and left well defined peripheries forming characteristic gyrate patterns. The buttocks showed a similar distribution. The eruption disappeared rapidly from the face and trunk but in some cases lasted six to fourteen days on the extremities, fading for hours or days and then reappearing. Rauh, Cincinnati.

Treatment of Eczema with Vitamin-B-Complex. K. P. Kristensen and S. N. Vendel, Lancet **1**:170 (Jan. 27) 1940.

The knowledge of allergy, hormones and vitamins has so far not solved the problems of the etiology, diagnosis and treatment of eczema. In a series of more than 100 unselected cases of eczema many different preparations of vitamin B complex were tried, some by mouth and some by injection. They seemed to be all

equally effective against eczema. Generally, in a week or ten days the acute eczema is healed. In about one or two weeks the chronic condition is definitely better. Although the factor concerned in the cause and cure of eczema in all probability resides in the vitamin B_2 complex, the authors obtained excellent results from the administration of the whole vitamin B complex.

LANGMANN, New York.

TWO COMMONLY MISUNDERSTOOD SKIN CONDITIONS IN INFANCY. I. GORDON, Brit. M. J. **1**:383 (March 9) 1940.

There is a brief discussion of "the scurfy head." The comment is made that there are two different conditions described under this term; i. e., milk crust and pityriasis capitis. A description of milk crust as largely a matter of lack of cleanliness is given. The other condition is pityriasis capitis, which is really simple dandruff, and for this the author suggests 1 per cent salicylic acid ointment. Next is discussed "napkin rash." This he discusses under several heads: first, "Ammoniacal Odour"; second, "Age Incidence" (the author stating that this rash occurs largely in infants under the age of 3 months); third, "Nocturnal Incidence"; fourth, "Social Incidence," and fifth, "Seasonal Incidence."

Mention is made of "meatal ulcer" due to the ammoniac diaper. The treatment is along the more or less conventional lines of rinsing the diaper in boric acid solution or applying boric acid ointment.

ROYSTER, University, Va.

LUPUS ERYTHEMATOSUS: THE EFFECTS OF SULFONAMIDES. H. W. BARBER, Lancet **1**:583 (March 30) 1940.

Lupus erythematosus in most of the cases met with in England is, in the belief of Barber, of streptococcic origin; in some cases the eruption may be a toxituberculide. When the disease has been apparently due to streptococcic infection, characteristic reactions to treatment with sulfanilamide and its derivatives have been observed, with subsequent benefit to the eruption in a high percentage of cases, whereas when a tuberculous infection was apparently responsible these reactions did not occur nor was the eruption affected.

LANGMANN, New York.

A CASE OF ACRODYNIA. G. C. PENICHET and A. G. LOPEZ, Bol. Soc. cubana de pediat. **12**:44 (Feb.) 1940.

The authors report acrodynia in a white child 8 months old. This is the third case of acrodynia to be reported in Cuba. Vitamin B therapy was without any effect. The authors give a comprehensive review of the theories regarding the causation of this disorder. The predominating theory seems to be in favor of a virus infection rather than a hormonal disturbance. The case terminated fatally. There was no autopsy.

SCHLUTZ, Chicago.

CREEPING DISEASE. O. SEIDL, Ztschr. f. Kinderh. **61**:257 (Aug. 9) 1939.

Creeping disease is apparently much less common in Europe than in America. The type seen in Europe is probably due to larvae, whereas the American type is probably due to nematodes. Clinical differences between the two types are mentioned. The author reports on the European type as observed in a 3 year old boy. A photograph shows the characteristic linear eruption. The daily progress of the eruption varies from 2 to 35 cm.

After numerous other forms of treatment had failed, the disease cleared up promptly after treatment by the method advocated by Le Sueur and Hutchinson (inunction with a mixture of oil of chenopodium and olive oil).

SIEMSEN, Chicago.

Teeth and Dentistry

MEAN ANNUAL HOURS OF SUNSHINE AND THE INCIDENCE OF DENTAL CARIES. B. R. EAST, Am. J. Pub. Health **29**:777 (July) 1939.

In a statistical study of 94,337 white boys, 12 to 14 years of age, living in rural and semirural areas, East found a mean incidence of dental caries of 353.5 per hundred boys during 1934-1935. The mean incidence of caries was found to vary inversely with the hours of sunshine prevailing in the areas of residence. The group variation of the incidence was from 290.5 to 485.75 per hundred boys, and the hours of sunshine varied from more to less than 3,000 to 2,200 in the four areas studied. The data suggest an inverse relation between the hours of sunshine and the incidence of caries in this sample of the population, but the author states that this relation is not necessarily causal. LIMPER, Louisville, Ky.

INHIBITION OF EXPERIMENTAL DENTAL CARIES BY FLUORINE IN THE ABSENCE OF SALIVA. V. D. CHEYNE, Proc. Soc. Exper. Biol. & Med. **43**:58 (Jan.) 1940.

A total of 76 rats were placed on a caries-producing diet; 32 had had the salivary glands removed, and 12 of these were given 3 mg. of fluorine in aqueous solution daily. As shown previously, the reduction of saliva greatly increased the incidence of caries. Normal animals on the caries-producing diet averaged 3.5 carious teeth per animal; those with salivary glands reduced averaged 10.5 and the desalivated rats receiving fluorine 2.3 carious teeth per animal. It appears that fluorine has a caries-inhibiting action even when oral secretions are at a minimum. HANSEN, Minneapolis.

DENTAL ANAESTHESIA IN CHILDREN: A COMPARISON OF VINYL ETHER AND ETHYL CHLORIDE IN A SERIES OF TWO HUNDRED CASES. J. O. FRENCH, M. L. HOOKER, R. B. VAUSE and A. L. ROBINSON, Brit. M. J. **1**:432 (March 16) 1940.

This is a discussion of the advantages and disadvantages of certain substances used for procuring dental anesthesia in children. The virtues and disadvantages of vinyl ether and ethyl chloride are discussed. The authors feel that both are safe and useful. The action of vinyl ether is shorter and less certain. It is possible that ethyl chloride is preferable, but it causes troublesome rigidity of the jaw. Ethyl chloride is slower and more likely to be accompanied by vomiting.

ROYSTER, University, Va.

INFANTILE MELANODONTIA. G. NOYER, Presse méd. **48**:286 (March 12) 1940.

Noyer calls attention to the condition seen often in the mouths of children between 1 and 4 years of age, in which the upper incisors appear as blackened stumps. This condition has been labeled caries, but there are several differentiating points. Caries appears in the fissures of the enamel or on opposing surfaces, produces an odor and gives rise to pain. Melanodontia rarely attacks other teeth, appears first in the middle third of the outer face of the upper incisors, produces no odor or pain and gives rise to no complications. The dentin is not involved, and the pulp cavity and root canal are not attacked. The black pigment is one of the melanins. The cause of this condition is probably a complex deficiency, lack of vitamin C playing a very important role. DAFFINEE, Boston.

FOCAL INFECTION OF DENTAL ORIGIN IN THE CHILD. V. DE LA MAZA and C. T. DEPASSIER, Rev. chilena de pediat. **11**:105 (March) 1940.

Focal infections of dental origin can be found in the deciduous teeth of children and are more common than is generally supposed.

Both dentists and pediatricians should pay more attention to the treatment of children's teeth. In this way many forms of focal infection can be prevented.

Many conditions ordinarily resistant to treatment clear up more rapidly when such foci are removed.

SCHLUTZ, Chicago.

DENTAL CARIES IN CHILDHOOD. H. VAN DER MOLEN and H. R. VAN DER MOLEN, Maandschr. v. kindergeneesk. **9**:318 (May) 1940.

The authors present a discussion of the different ways in which dental caries in childhood arises and of the great significance of the prevention of caries by regulation of the diet, combined with regular examination of the teeth every three or six months from the age of 3 years on. To prevent caries of the milk teeth a good regulation of the diet of the pregnant woman is necessary, and food rich in vitamins and poor in sugar during childhood is necessary to keep the teeth in good condition.

VAN CREVELD, Amsterdam; Netherlands.

Miscellaneous

SCAEVOLA OF SAINTE-MARTHE AND THE PAEDOTROPHIA. G. K. TALLMADGE, Bull. Hist. Med. **7**:279 (March) 1939.

This is a very complete work of 35 pages on Scaevola of Sainte-Marthe and his famous work. The biographic portion includes the family history back to the fourteenth century, the author's youth, his schooling, his interest in poetry, law and theology, and his political career. Scaevola was not a physician, but he had acquired a great deal of knowledge on the nature and care of infants in trying to cure his own son after the latter had sought help in vain from many physicians. Urged to preserve the fruits of his research for posterity, he produced, in 1584, the "Paedotrophia," a didactic poem, written in Latin, in three books, totaling 1,726 lines. It was approved by the medical faculty of Poitiers, France, and appeared in ten editions during his lifetime. By 1795, ten foreign editions had appeared. The first English translation was printed in 1708; the much better second one, by H. W. Tytler, in 1797.

The "Paedotrophia" is a "mélange of fable, history, philosophy and medicine," but contains much good advice and many good ideas. Tallmadge proceeds to give the substance of the work, often complemented by actual translations, thus bringing this work, which is difficult to read, much closer to present day physicians. One reads of the advisability of nursing, prenatal care, birth marks, asphyxia neonatorum, rules governing the choice of a wetnurse, weaning, feeding in later infancy, sleep, bath, exercise, discipline. Many pathologic conditions are discussed, as changes of the umbilical cord, tongue-tie, ranula, stomatitis, tonsillitis, diarrhea, etc., to mention a few. He differentiated between chickenpox and smallpox.

Facsimiles of the page with the opening lines, the approbation of the faculty of medicine of Poitiers, and the title page of Tytler's English edition (1797) illustrate the article.

ROSENTHAL, St. Paul.

A NOTE ON EDWARD JENNER'S LOST MANUSCRIPT ON "RHEUMATISM OF THE HEART." H. KEIL, Bull. Hist. Med. **7**:409 (April) 1939.

On July 29, 1789 Jenner read a paper on "Rheumatism of the Heart," illustrated by dissections, before the Fleece or Glouchestershire Society. This paper apparently was never published and has not come to light. A hundred years ago J. Baron, Jenner's biographer, stated that this paper "contained observations respecting a disease of the heart which frequently comes on during attacks of acute rheumatism, and leads to enlargement and disorganization of the part. This formidable disorder had very much escaped notice of medical men. Jenner's

observations were original, and had they been published at the time they were first communicated to the Society, his claims to priority could not have been set aside as they have since that time by other writers." This again shows Jenner as a gifted pathologist.

ROSENTHAL, St. Paul.

THE NURSING CAN: AN EARLY AMERICAN INFANT FEEDING DEVICE. H. DITTRICK, Bull. Hist. Med. **7**:696 (July) 1939.

Dittrick furnishes a description of a characteristic nursing can, the use of which apparently was limited to Pennsylvania. The capacity of such cans usually ranged from 150 to 170 cc., though an occasional one reached 390 cc.; the usual height was about 10 cm.; the diameter at the base was about 6 cm., the can tapering toward the top. It was made of tin and had a flat handle and a convex cap. A spout on the side ended in a rounded knob and communicated with a vertical tube inside the can. This tube was either closed on top or open.

The author was unable to trace the origin of the nursing can, but feels that it was inspired by a feeding device of the type of Hugh Smith's "bubby-pot." It seems that it was introduced into Pennsylvania by German settlers in the late eighteenth century, and its use could be confirmed for as late as 1868.

ROSENTHAL, St. Paul.

THE FORMATION OF METHEMOGLOBIN AND SULFHEMOGLOBIN DURING SULFANILAMIDE THERAPY. J. S. HARRIS and H. O. MICHEL, J. Clin. Investigation **18**:507 (Sept.) 1939.

Nine hundred and sixty blood samples from 476 patients receiving sulfanilamide were examined for free sulfanilamide content, methemoglobin and sulfhemoglobin.

The average methemoglobin value of all bloods was proportional to the sulfanilamide concentration. Methemoglobinemia was somewhat more frequent and more pronounced in the very young. Sulfhemoglobinemia was more frequent after long courses of sulfanilamide but did not bear any relation to age, sex or the concentration of sulfanilamide or of methemoglobin in the blood.

GUEST, Cincinnati.

SOME ASPECTS OF THE PHARMACOLOGY OF SULFAPYRIDINE. E. K. MARSHALL JR. and J. T. LITCHFIELD JR., J. Pharmacol. & Exper. Therap. **67**:454 (Dec.) 1939.

This excellent work is probably best summarized by the authors' own summary.

"1. Sulfapyridine is more toxic than sulfanilamide for mice, rabbits and dogs on the basis of blood concentration of the drug. Likewise, acetylsulfapyridine is more toxic than acetylsulfanilamide.

"2. Sulfapyridine, although apparently no more depressant to renal functions in dogs than sulfanilamide, in its conjugated form as acetylsulfapyridine may cause a marked lowering of kidney function as measured by creatinine clearance.

"3. The absorption of sulfapyridine from the gastrointestinal tract is slower, less complete and more variable than is that of sulfanilamide under the same conditions. The physical state as well as the solubility of the preparation used influence absorption.

"4. Sulfapyridine resembles sulfanilamide in its ready penetration to all tissues and body fluids in a concentration not far removed from that of the blood. However, unlike sulfanilamide it is usually present in higher concentration in the liver than in other tissues; and, in addition, there is more variability in its distribution from animal to animal.

"5. The mode of excretion of sulfapyridine by the kidney appears to resemble very closely that of sulanilamide."

PILCHER, Cleveland.

DEVELOPMENTS IN PEDIATRICS IN THE PAST QUARTER CENTURY. G. P. POWERS, Yale J. Biol. & Med. **12**:1 (Oct.) 1939.

Powers groups the entire material under eight titles: "Supportive Therapy" (parenteral fluid and electrolyte supply, blood transfusions); "Infant Feeding and Nutrition" (simplification of infant feeding, hygiene, "cholera infantum," vitamins, etc.); "Infectious Diseases"; "The Newborn"; "Behavior Problems"; "Mental Deficiency"; "Preventive Pediatrics," and "The Future of Pediatrics." Five tables and three charts supply statistical material. ROSENTHAL, St. Paul.

EVALUATION OF SHORT-WAVE DIATHERMY. RICHARD KOVACS, Brit. J. Phys. Med. **3**:5 (Jan.) 1940.

The clinical uses of long wave diathermy and short wave diathermy are, in the main, identical. Preference may be given to the former for localized treatment of bursae and of some joints, as well as for orificial work. The claim of specific effects of short wave diathermy in the treatment of localized suppurative conditions is still awaiting convincing clinical corroboration. HARTMAN, Cleveland.

THE FATE IN THE BODY OF SULFAPYRIDINE. A. J. CLARK, Edinburgh M. J. **47**:241 (April) 1940.

Therapy with this drug has produced one triumph after another, but there is the problem of toxic side actions, although dangerous ones are rare. The writer discusses the fact that most of the drug present in the blood is in the free form, while much which is excreted is in the conjugated form, indicating that the latter undergoes excretion more quickly than does the free drug. It is the free form which exerts the therapeutic influence. The action of the free drug therefore is steadily reduced by acetylation in the liver and excretion by the kidney. Absorption of the drug is slower in patients with fever than in healthy persons, the latter absorbing most of the drug within four hours. As there is slight absorption within the stomach, the appropriation of the drug is dependent on the emptying rate of the stomach, which of course varies much in the presence of disease. The author states that since it is agreed that the acetylated drug is toxic and without therapeutic effect, it would be profitable to study the relation between the blood concentration of the acetylated form and the incidence of toxic effects.

NEFF, Kansas City, Mo.

DOSAGE OF SULPHANILAMIDE DERIVATIVES FOR CHILDREN. M. HYNES, Lancet **1**:261 (Feb. 10) 1940.

It is agreed that sulfanilamide therapy gives the best results when the concentration of the drug in the blood is 4 to 10 mg. per hundred cubic centimeters. It is therefore important to know what dosage will produce this concentration. This question was investigated in children, of whom 64 received sulfapyridine (2-[para-aminobenzenesulfonamido]-pyridine; preparation used M. & B. 693); 13 sulfanilamide and 4 proseptasine (parabenzylaminobenzenesulfonamide).

A table is given suggesting the dosage at various ages, but for best results the dosage must nevertheless be controlled by determinations of the concentration of the drug in the blood. LANGMANN, New York.

BESNIER-BOECK'S DISEASE OR BENIGN LYMPHGRANULOMATOSIS OF SCHAUMANN (THE BESNIER-BOECK-SCHAUMANN SYNDROME). C. G. LAMBIE, M. J. Australia **1**:815 (June 15) 1940.

Lambie emphasizes the fact that Besnier-Boeck's disease is a generalized condition, involving the skin, bones, lymphatic organs, eyes, lungs and other viscera, and presents 8 case records in which the outstanding common feature was the presence of disseminated lesions in the lungs roentgenologically resembling those

of miliary tuberculosis. Since accumulations of epithelioid cells constitute an invariable feature of Besnier-Boeck's disease wherever they occur in the body, it is evident that the disease is essentially reticuloendotheliosis. There are three schools of thought regarding the cause of the disease. According to one it is a form of tuberculosis; another holds that it is a pathologic entity; a third regards it as a nonspecific tissue reaction to a number of different causes. The various clinical manifestations of the disease are fully discussed. GONCE, Madison, Wis.

THE DISEASES AND HYGIENE OF INFANTS AND CHILDREN IN 1939. P. LEREBOULLET, Paris méd. **2**:285 (Dec. 2-9) 1939.

This review is divided into four parts. The first is introductory and explains that because of the press of work related to the war the author is unable to make his usual analytic review of the progress in pediatrics for the past year. In the second section he discusses briefly the hygiene of infancy and childhood. The third section is given over to a consideration of the decreased birth rate in France and its consequences. The fourth takes up the problem of sanitation in relation to refugee children.

LESLIE, Evanston, Ill.

STERNAL PUNCTURE IN THE CLINIC. M. MANGUEL, Rev. méd. latino-am. **25**:576 (Feb.) 1940.

Sternal puncture for the study of bone marrow is an easy and valuable diagnostic procedure. The sternum is penetrated at a point between the second and third intercostal spaces. The technic is described in detail. The author records the normal hemogram, as well as the findings in leukemia, purpura, medullary tumors, kala-azar, malaria and disturbances of lipoid metabolism.

DWYER, Kansas City, Mo.

EXTRAUTERINE PREGNANCY OF TWENTY-ONE MONTHS' DURATION. CHUNG CH'UNG-TE, Chinese M. J. **47**:184 (Feb.) 1940.

A dead fetus weighing 1,980 Gm. was delivered by opening the peritoneum by a low midline incision. The fetal membrane had been attached to the fallopian tube. The mother recovered.

NEFF, Kansas City, Mo.

News and Comment

UNIVERSITY NEWS

Louisiana State University.—Dr. Chester A. Stewart, clinical professor of pediatrics at the University of Minnesota Medical School, has been appointed professor and head of the department of pediatrics in the Louisiana State University School of Medicine, the appointment to be effective July 1.

Society Transactions

CHICAGO PEDIATRIC SOCIETY

PHILIP ROSENBLUM, M.D., *President*

BENGT HAMILTON, M.D., *Secretary*

Regular Meeting, Oct. 15, 1940

Quantitative Estimation of the Pyruvic Acid Content of the Blood in Infants and Children: An Attempt to Diagnose Subclinical Deficiency of Vitamin B_1. DR. KATSUJI KATO and DR. PEI-KUANG LI (by invitation).

This article will be published in full in a later issue of the AMERICAN JOURNAL OF DISEASES OF CHILDREN.

Spontaneous Pneumomediastinum in the Newborn Infant. DR. B. GUMBINER and DR. MEYER M. CUTLER.

The clinical entity of pneumomediastinum, or mediastinal emphysema, has been described for many years. Numerous cases of the disorder in infants and in adults have been reported, but relatively few reports have mentioned its occurrence in newborn infants. The few cases reported either do not mention or fail to stress the pathognomonic roentgen picture, especially as visualized on lateral projection. Furthermore, aspiration as a possible therapeutic procedure has never been performed.

Our first case was seen in March 1940. A diagnosis of tense pneumomediastinum was made, and because of the critical condition of the infant therapeutic aspiration of the mediastinum was done. This procedure was followed by complete recovery within three days. Diagnosis in this case was possible because a lateral roentgenogram was made; and as this procedure is not commonly carried out in the examination of newborn infants, it is our belief that the diagnosis may be missed in a certain percentage of cases. During the next four months, in a series of 23 roentgen examinations of newborn infants, 3 additional cases were discovered.

(Illustrative roentgenograms were shown.)

Clinically, the condition is characterized by the sudden appearance of respiratory distress and varying degrees of cyanosis, with or without such signs as distention of the veins of the neck, bulging of the precordium, distant heart tones, obliteration of cardiac dulness, a crackling sound synchronous with the heart beat, subcutaneous emphysema or indications of pneumothorax.

The diagnosis is established through roentgenograms of the chest, and it should be stressed that there are pathognomonic features evident in those taken from the lateral view.

Macklin's experimental work revealed that the cause of pneumomediastinum is overdistention of the lung and that the air from the ruptured alveoli passes along the vascular sheaths to the mediastinum.

It appears likely, from experimental and from clinical observations, that pneumomediastinum may secondarily result in pneumothorax, pneumoperitoneum or subcutaneous emphysema.

As a general rule, treatment should be conservative, with such administration of oxygen and stimulants as may be necessary; but increasing dyspnea and cyanosis are an indication for therapeutic aspiration.

Pneumomediastinum in the newborn is apparently not rare, and its recognition and treatment should decrease neonatal mortality.

DISCUSSION

DR. EDWIN J. DE COSTA: Dr. Gumbiner and Dr. Cutler should be congratulated for their presentation of material about a disorder which probably occurs frequently but is either unrecognized or misdiagnosed. My interest in this problem arose when I saw 2 babies with spontaneous pneumothorax within one month. In the literature I found references to 48 similar instances associated with birth. The slide which I wish to show is of particular interest. It was made from a roentgenogram taken in the lateral view, as advocated by Dr. Gumbiner and Dr. Cutler, and shows fairly well the presence of air in the upper part of the mediastinum, in the subcutaneous tissue and in the peritoneal cavity.

My interest in the mechanics of production of this condition led to a series of animal experiments which conclusively substantiated the work of Macklin; they demonstrated that the air primarily spreads from the alveoli to the mediastinum along the perivascular sheaths. It may remain in the mediastinum, and if the pressure increases it may cause the symptoms discussed here this evening. Or it may spread upward along the vessels into the subcutaneous tissue of the neck or downward into the peritoneal cavity, or it may rupture through the mediastinum into the pleural cavity. That this mechanism actually exists is proved by the occurrence of mediastinal emphysema, followed by pneumothorax, with clinical relief of the symptoms caused by mediastinal pressure.

What causes the air to escape from the alveolus? The answer is: any increase in intrapulmonic pressure. However, it must be remembered that variation in the tissue itself will determine the pressure necessary for escape from the alveolus to occur, and the pressure requirements, at least in dogs, are variable. What may lead to an increase in intrapulmonic tension? Briefly, one may list such causes as the presence of mucus, vernix or meconium in the air passages; struma; enlargement of the thymus; wrapping of the umbilical cord around the neck, and, most important, any form of artificial respiration. It is significant that in 57 per cent of my series of cases of spontaneous pneumothorax in which the disorder was of the severe, acute type there was a history of administration of some type of artificial respiration. The dangers of improper insufflation must be borne in mind. It has been shown that pneumomediastinum is the forerunner of subcutaneous emphysema, spontaneous pneumothorax and the rarer spontaneous pneumoperitoneum. It must therefore occur fairly frequently and probably is responsible for many deaths that are attributed to atelectasis.

DR. NOEL SHAW: I should like to know if a Henderson or a Drinker respirator was used in any of these cases mentioned by Dr. Gumbiner.

DR. B. GUMBINER: In reply to Dr. Shaw, no Drinker respirator or other method of artificial respiration was used in any of the cases, and there was no record of the use of the tracheal catheter. However, the catheter is commonly employed for clearing the air passages; so it is probable that it was used in our cases.

Auricular Fibrillation in Childhood and Adolescence. DR. STANLEY GIBSON.

Among 864 patients with rheumatic heart disease, 21 instances of auricular fibrillation were encountered. In all cases there was evidence of mitral damage, as well as cardiac enlargement, which in the majority of cases was marked. Congestive heart failure was present in 18 of the 21 cases at the time of onset of auricular fibrillation. There was no relation between the length of time that had elapsed since the first rheumatic episode and the onset of fibrillation, which rarely occurred before the tenth year of life. In 3 cases the onset of auricular fibrillation appeared to have resulted from the administration of digitalis. In all 3 there was a return to normal rhythm a few days after digitalis was withdrawn.

In 14 of the 21 cases the patient is known to have died, and in 3 others the patient was in a critical condition when last seen. In the group of patients from 9 to 12 years of age, the average length of life after the onset of fibrillation was eight months, whereas for the teen-age children who have died it was twenty-nine months.

DISCUSSION

DR. ARTHUR F. ABT: I have had charge of about 300 children with cardiac disorders at the Spaulding School during the past five or ten years. I can recall that approximately 10 of the children who regularly attended school had auricular fibrillation. The first children with fibrillation whom I examined rather terrified me. I thought that perhaps they should not attend school. I asked the nurses in charge to observe them closely and found that they were able to continue their school work and get along as well as the other children with cardiac disorders who had regular rhythms.

Some of these children with fibrillation have gone from grammar school through high school. So far as I could judge, they were able to tolerate the activity and to complete the courses as well as the other pupils with cardiac disorders.

Before I had the opportunity to observe these children, I was inclined to believe that the prognosis in cases of auricular fibrillation in childhood was as ominous as Dr. Gibson has indicated tonight. Perhaps the explanation for this difference in viewpoint is that in one series of cases the children had had recent or recurrent attacks of acute carditis, while in the other there had been no recent carditis and the fibrillation accompanied an inactive phase of the disease.

It will be interesting to know the ultimate destiny of the children at the Spaulding School who are under my observation.

DR. JAMES H. WALLACE: I think the role of digitalis in these cases is interesting. Dr. Gibson suggested that digitalis might induce fibrillation; yet it is a valuable drug for keeping down the cardiac rate. In some cases the required dosage is extremely unpredictable. Sometimes with the start of fibrillation in childhood, and especially in adolescence, the increased heart rate may lead to congestive failure. Digitalis may bring the rate down, so that the heart may become compensated and, as Dr. Gibson and Dr. Abt suggested, the patient may be able to carry on a fairly active life. Some children may need 1.5 grains (0.1 Gm.) daily to hold the rate in the 90's, while others may achieve the same result by taking the same amount every three or four days. It is paradoxic that digitalis can stimulate fibrillation and yet at the same time be a factor in keeping the cardiac rate down.

DR. L. N. KATZ: Dr. Gibson's interesting report is an important contribution to the knowledge of the subject of auricular fibrillation. A great deal is known about this condition in adults, but information about the disease in children is meager. Dr. Gibson's report helps to fill in the gap. The experience of my associates and me during the last ten years at Michael Reese Hospital coincides with that of Dr. Gibson so far as prognosis is concerned, rather than with that of Dr. Abt. The fact that digitalis can provoke auricular fibrillation in the adult in some cases is well known. Patients with active rheumatic fever are more sensitive to digitalis than others; hence great care should be used in administering digitalis to such a patient. Auricular fibrillation is readily produced in such patients by digitalis. If digitalis causes auricular fibrillation, it should be stopped. If the drug is not the cause of the fibrillation and the ventricular rate is rapid, it should be administered until such time as the ventricular rate is reduced to about 80. Striking improvement in the cardiac failure may be brought about by this means, even in the presence of acute rheumatic fever.

Auricular fibrillation is to be viewed as a late event in the natural history of rheumatic fever. Since the whole course of the disease is shorter in children than in adults, the life expectancy for a child with auricular fibrillation would be less than for an adult. It must be borne in mind that cases of "benign" auricular

fibrillation in adults have been reported in which the disorder persisted for as long as twenty years. Consequently, in not every case of auricular fibrillation in a child would an abbreviated life expectancy be justified.

I should like to ask Dr. Gibson if any of his patients had embolic phenomena resulting from the release of emboli from thrombi in the auricles.

One reason auricular fibrillation is so rare in children, it seems to me, is that their auricles are small. It is easier to produce fibrillation in a large auricle than in a small one. This point can be illustrated by considering animals of different sizes. For example, it is easier to induce and maintain auricular fibrillation in the dog than in the rat. It seems, then, that enlargement of the auricle, such as when there is advanced mitral disease and especially when there is myocardial disease in the auricles themselves, is a condition which is optimum for the production of auricular fibrillation.

DR. ROBERT HERZOG: I should like to acknowledge my appreciation of Dr. Gibson's stimulating paper. In previous years I saw some children with auricular fibrillation at the Sunset Cardiac Camp. The striking thing about this group of patients was that nearly all had cardiac enlargement and active infection at the time the fibrillation was discovered or shortly afterward. Established fibrillation nearly always has serious implications.

Incidentally, I think Dr. Abt ought to make his survey quickly, because during every six months he delays the number of children he will have to follow up will be reduced. In the Christopher School, during the time I had charge of the cardiac clinic there, there were no children with auricular fibrillation because I felt that such children had too serious a handicap to permit attendance at even a special school.

I have seen, however, 2 instances of what appeared to be paroxysmal auricular fibrillation in children with quiescent heart disease. Both occurred while the children were at Sunset Camp. In 1 child the attack lasted about twelve hours, and there has been no suspected recurrence of either fibrillation or active infection in seven years. The other child had fibrillation for about eight hours and had no recurrence for at least two years, after which time I lost track of her.

It might be worth stressing that in the management of children with auricular fibrillation and in deciding whether there has been enough rest and whether the digitalis dosage has been adequate, the ventricular rate ought to be as good a guide as it is in the case of adults. Even though the patient has fibrillation, the ventricular rate is still influenced by many of the factors which normally affect the heart rate. Sympathetic-parasympathetic effects still operate through the auriculoventricular node, although the sinoauricular node may be said to be uninfluential. This may explain, in part, some of the paradoxes in the clinical use of digitalis in cases of auricular fibrillation.

Of Dr. Gibson's 864 patients with rheumatic heart disease, 2.5 per cent had fibrillation. Among the patients attending the cardiac clinic for adolescents of Michael Reese Hospital, the incidence of patients with auricular fibrillation would be between 2 and 3 per cent; I cannot give the exact figure offhand.

DR. STANLEY GIBSON: In regard to Dr. Abt's series of cases, I should like to know three things: whether the clinical diagnosis was checked by an electrocardiographic examination, the age of the child at the onset of the auricular fibrillation and the length of time that fibrillation has been present. It is true that children of high school age may go along fairly comfortably for a few years. It has been my experience that younger children are seldom able to be up and about after the onset of fibrillation.

I agree with Dr. Katz that digitalis should be withdrawn if it seems to have produced auricular fibrillation and that it is often of great value and should be used as necessary to control the heart rate in cases in which the fibrillation has arisen spontaneously. In reply to Dr. Katz's question concerning embolic phenomena, 1 of my patients suffered hemiplegia about six months before death.

PHILIP ROSENBLUM, M.D., *President*

BENGT HAMILTON, M.D., *Secretary*

Regular Meeting, Nov. 12, 1940

The Serum Therapy of Tetanus. DR. RALPH SPAETH.

This article will be published in full, with discussion, in a later issue of the AMERICAN JOURNAL OF DISEASES OF CHILDREN.

Erythroblastic Anemia: A Clinical Study. DR. MILA I. PIERCE.

Fifteen cases of Cooley's erythroblastic anemia are reported from Children's Memorial Hospital, with photographs and roentgenograms showing the characteristic physical and bone changes. The significant hematologic features and the observations on bone marrow are discussed. Graphs are presented illustrating the failure of the anemia to respond to iron, liver extract, quinine and splenectomy. Transfusions are shown to be of only temporary value. Evidence is presented that parents who are carriers of the disease may be detected by the results of fragility tests; such parents have abnormally resistant erythrocytes. The pathologic characters are briefly discussed. It is pointed out that until more detailed knowledge is available concerning the function of the reticulum cells and until the maturation factors related to erythropoiesis are understood, the pathologic features of erythroblastic anemia cannot be fully appreciated.

Diagnosis and Management of Convulsions in Childhood. DR. A. LEVINSON and DR. M. A. PERLSTEIN.

Some physicians minimize the importance of convulsions in children. No less an authority than Cameron stated in his book "The Nervous Child," "Habit spasm, bed-wetting, sleep-walking, night terrors, and convulsions are symptoms which are frequent enough in children, and there is no need to be unduly alarmed at their occurrence." The reason convulsions in children are not always considered of serious import is because they occur frequently at the onset of acute infectious disease and may never recur.

Experience has shown that every convulsion in a child should be taken seriously. Not all convulsions accompanied by fever are transitory. They may be caused by meningitis, encephalitis and tumors and other organic abnormalities of the brain. Of the 408 cases studied by us, in 24 per cent the convulsions were due to epilepsy. Furthermore, in many of our cases of epilepsy the first convulsion occurred during infancy, sometimes accompanied by fever. No one can tell, therefore, that a convulsion may not be the beginning of epilepsy. However, even if the convulsions do not recur, does that mean that they are of no significance? The fact that they occur in some children and not in others speaks for some anatomic or functional abnormality in those who have them.

What is the cause of the so-called functional convulsions?

With the increasing knowledge about the metabolism of calcium and phosphorus, it seemed probable that functional, like tetanic, convulsions were due to calciprivia. Most of our cases do not bear out this contention. The levels of calcium and phosphorus in our cases have practically always been normal unless the convulsions were due to tetany. Further research in that direction, however, is necessary. We have found some changes in the cerebrospinal fluid after the convulsions accompany many acute transitory cerebral disorders. There are a high cerebrospinal fluid pressure and a high level of sugar. The high pressure is most likely caused by the cerebral edema which accompanies all convulsions, and the high cerebrospinal sugar is due to the high concentration of blood sugar which is present in all febrile conditions because of the increased metabolism.

It seems not unlikely that children who get convulsions on the slightest provocation may have a general cerebral instability due to cerebral birth trauma, to anoxia or to hereditary susceptibility, in other words, to an "anlage" of cerebral

dysrhythmia. In these children a disturbance of balance in the nervous system can be caused by hyperthermia or even by a disturbance of the gastrointestinal tract. This condition could be considered akin to spasmophilia except that the latter disorder is due to a low level of calcium in the blood.

No matter what the cause, convulsions should be stopped as soon as possible. Every convulsion should be considered a pediatric emergency. The administration of chloroform remains the best emergency measure. It has its drawbacks, the most important being the danger of burns; but if care is taken not to tighten the mask and if petrolatum is applied around the face, the chances of a patient's being burned are small. I never saw a death caused by chloroform.

For the prevention of convulsions chloral hydrate, with or without bromide, is a useful drug if it is given in large enough doses. Attention is called to the high blood sugar that follows the administration of chloral hydrate; it must not be confused with a true diabetic hyperglycemia. From the standpoint of practicability, capsules of 1.5 grains (0.1 Gm.) of pentobarbital sodium or sodium propylmethylcarbinylallylbarbiturate (seconal), which are easily carried in the bag or pocket, are useful for the prevention of convulsions. The capsule is perforated and introduced into the rectum. For an infant weighing 14 to 15 pounds (6.4 to 6.8 Kg.) 1 capsule suffices, since it provides a dosage of 0.1 grain per pound (0.006 Gm. per 454 Gm.) of body weight. For older children 2 capsules may be needed.

The introduction of a mouth gag during a convulsion not only is unnecessary but may be harmful. It is so difficult to open the child's mouth during a spasm that trauma may ensue from the attempt. There have been cases in which one or more teeth were knocked out by the introduction of a mouth gag, and in 1 instance there was a fracture of the jaw. Biting the tongue is undesirable, but the danger from it is not so great as from fracturing the jaw.

Should spinal puncture be performed during or after a convulsion? It should never be performed during the convulsion because of the possibility of herniation of the brain. Whether puncture should be performed immediately after the convulsion depends on the probable diagnosis. If meningeal signs are present, it is important to do the puncture in order to decide whether meningitis is present and if it is present to determine its type. If meningitis is not suspected, spinal puncture should not be performed for two or three days, if at all, unless there is increased intracranial pressure which cannot be reduced by drugs. There are two reasons for delaying puncture. First, during the postconvulsive state, which may last for two or three days, the spinal fluid may furnish false information; often there is an increase in cells and in protein merely because of the irritation of the meninges by the convulsions. Second, the child should not be disturbed after a convulsion.

As a matter of fact, it is inadvisable to make more than a cursory examination of a child immediately after a convulsion, first, because the information obtained from the examination may be misleading, since the patient is often dazed, does not respond properly and may even have temporary paralysis, and second, because it is wrong to disturb a patient who is in shock.

PHILIP ROSENBLUM, M.D., *President*

BENGT HAMILTON, M.D., *Secretary*

Regular Meeting, Dec. 17, 1940

An Evaluation of Pertussis Vaccination by Clinical Means and by the Opsonocytophagic Test. DR. ALWIN C. RAMBAR, DR. KATHERINE HOWELL and MR. MORRIS GOLDMAN.

An evaluation of immunization against pertussis by means of clinical and immunologic studies is reported. In the clinical part of the study 379 children,

varying in age from 6 months to 5 years, were given injections at weekly intervals which totaled 8 cc. of a suspension of hemolytic pertussis organisms in phase I (10,000,000,000 per cubic centimeter). One hundred and forty unvaccinated siblings served as controls. Nine of the 58 vaccinated children who were known to have been exposed to whooping cough contracted the disease, an incidence of 15.5 per cent. Thirty-seven of the 47 controls who were known to have been exposed to whooping cough contracted the disease, an incidence of 78.7 per cent. The children in the vaccinated group, in general, had a milder form of pertussis than did those who were unvaccinated.

These results indicate that there is a definite reduction in the incidence and the severity of whooping cough after vaccination with a preparation of hemolytic pertussis organisms in phase I.

Of the laboratory methods which have been suggested to determine immunity to pertussis—complement fixation, agglutination, specific cutaneous testing and the opsonocytophagic test—the last named was chosen because it can be performed readily with a minimal amount of blood and because it appeared to offer promise of being a reliable index of immunity. The technic and the results of this test are described.

It is believed that this study indicates both clinically and immunologically that vaccination is of definite value in reducing the incidence of whooping cough, that revaccination two years after the original inoculation is a desirable procedure and that the opsonocytophagic test gives a reliable index of immunity.

Vaccination Against Whooping Cough in Early Infancy. Dr. L. Sauer, M.D.

Each year for seven years, about 200 infants in the Cradle, in Evanston, Ill., who were less than 3 months of age were given injections of Haemophilus pertussis vaccine. They stood the injections well. The rectal temperature rarely exceeded 38.5 C. (101.3 F.), and local reactions were usually negligible. Local induration or a subcutaneous nodule occasionally persisted for a week or two, but in no instance did a local abscess occur.

On Jan. 1, 1940 the director of the Cradle mailed a questionnaire to the foster parents of the 1,434 children who had been given injections before the third month of life. This report deals in the main with the data gathered from the 1,110 questionnaires which were returned. The average age of the children at the time of the investigation was about 4 years. Sixty-eight of the 91 in whom pertussis had developed were in families which had no older children.

For comparison Dr. James P. Campbell compiled data on the attack rate of pertussis among the children born in the Community Hospital, Geneva, Ill., located 45 miles (72.5 kilometers) from Chicago. Somewhat less than 200 infants are born there annually. On Jan. 1, 1940 the hospital superintendent mailed a questionnaire to the parents of 1,000 living children who had been born at the hospital during the previous seven years. Data were received on 464 of them; 256 had not had any vaccine; 208 had been inoculated with H. pertussis vaccine after the age of 7 months. The average age at the time the questionnaire was answered was somewhat less than 4 years.

The data on the children in Geneva who had been vaccinated against pertussis after the seventh month of life by various physicians served as an independent substantiation of the data compiled by the Evanston Health Department Clinic during the past six years and of the data on private patients who were vaccinated after the seventh month of life. Eighty-five per cent of the vaccinated children who contracted whooping cough were given injections of vaccine made in 1934. The mildness of the disease in the children from the Cradle vaccinated since 1935 leads to the assumption that even when the vaccine, which was injected during the first months of life, failed to prevent pertussis, it did serve to reduce the danger of complications. No death from whooping cough has been reported for a child who contracted the disease after receiving injections of vaccine.

In summary, pertussis developed in 14.84 per cent of the children in Geneva (controls) who had had no vaccine; in 9.09 per cent of the children from the Cradle, who were vaccinated before the third month of life; in 2.48 per cent of the private patients in Evanston, who were vaccinated after the seventh month of life, and in 1.44 per cent of the children in Geneva, who were vaccinated after the seventh month of life.

Conclusion.—Pertussis occurred seven times more frequently among children vaccinated before the third month of life than among those vaccinated after the seventh month of life.

DISCUSSION ON PAPERS BY DRS. RAMBAR AND HOWELL AND MR. GOLDMAN AND DR. SAUER

DR. JAMES H. WALLACE: As I understand the paper by Dr. Rambar and his associates, the titer of the blood for the group of children who had had whooping cough, when determined several years afterward, had dropped to a low level. I wonder how that fits in with clinical experience, for it is certainly unusual for a patient to have a second attack of whooping cough.

DR. I. M. LEVIN: Dr. Rambar and his associates are to be congratulated on this excellent paper. If the opsonocytophagic index reflects the immunity to pertussis, the test will be of much value. The value of cutaneous tests have not been established; in particular, the work of the Italian Garzia has not been corroborated. With reference to the use of adult blood, I have seen several instances in which a mother furnishing blood contracted whooping cough at the same time as her child who had been exposed to the disease. The most significant part of this work is that two or three years after immunization one can inject pertussis vaccine and raise the titer of the blood to a level that will protect the patient adequately. This phenomenon was well described by Hall, who showed that after two injections of tetanus toxoid a third injection given after eighteen months raised the serum titer from 0.04 unit per cubic centimeter to as much as 15 or 20 units. For this reason, all children who have been immunized with vaccine should receive an additional injection after one or two years; possibly yearly repetition would be best.

DR. M. L. SPIVEK: I should like to ask one question on a point which was not covered in Dr. Sauer's paper. During the period of immunization against whooping cough, has a severe cough ever developed which might be mistaken for whooping cough? I have not observed such a cough, but it has been said to occur.

DR. LOUIS W. SAUER: In reply to Dr. Spivek, I have not encountered the reaction he mentioned.

Book Reviews

Special Surgery in War Time. Edited by Sir Humphry Rolleston and Alan Moncrieff. Price, 6s. net. Pp. 74, with no illustrations. London: *The Practitioner,* in conjunction with Eyre & Spottiswoode, Ltd., 1940.

This is the second of the booklets published by *The Practitioner,* which are under the general editorship of Sir Humphry Rolleston and Alan Moncrieff. It is composed of five short articles dealing with surgical subjects and is written to bring out the application of the accepted principles of diagnosis and treatment to special war injuries.

The first section deals with head injuries and is contributed by D. W. C. Northfield. It comprises an excellent summary of present day conceptions. The discussion of the treatment of open head injuries is informative and practical.

The second section, by Douglas McAlpine, concerns the diagnosis and treatment of injuries to the spinal cord, with a valuable paragraph on first aid treatment.

V. Zachary Cope has written the third section, which describes methods for the diagnosis and the treatment of abdominal injuries and wounds. Dr. Cope has condensed a large amount of important information into a small space.

The fourth section, by T. Holmes Sellors, is on thoracic injuries in modern warfare. In the fifth section A. B. Wallace describes various methods of treating burns, giving preference to that employing tannic acid and silver nitrate. An appendix deals with the prophylactic and therapeutic use of sulfanilamide and its derivatives in wartime.

This booklet is full of practical information and is to be warmly recommended. It is to be hoped that the editors will soon bring out other booklets on surgical problems in wartime.

Clinical Urology. By Dr. Oswald Swinney Lowsley and Dr. Thomas Joseph Kirwin. Two volumes. Price, $10 per set. Pp. 1,684, with 365 illustrations. Baltimore: Williams & Wilkins Company, 1940.

This is a work on general urology in two volumes, designed primarily for medical students. The first five chapters of volume 1 cover the general aspects of urologic examinations. They explain in detail the various laboratory, roentgenologic and instrumental equipment needed to make such examinations. Instructions are given for the oral administration of hippuran (sodium orthoiodohippurate) for obtaining excretory urograms in children. Good pictures have been obtained and no reactions noted with this method. However, the procedure is time consuming and impractical in clinic practice.

Anomalies of the urinary and the genital tract are recorded, and their treatment is outlined. In the chapters devoted to infections of the male and female genitalia, the use of sulfanilamide and its related compounds is considered.

Prostatism is fully discussed, and the authors have arrived at definite opinions regarding its treatment. Perineal prostatectomy appears to be the senior author's procedure of choice for treating enlargement of the prostate, with retention of urine or evidence of absorption of pus from the gland, and for relieving pain. Transurethral resection is reserved for moderate enlargement or carcinoma of the prostate and for fibrosis of the vesical neck.

Enuresis in children is discussed mainly from the standpoint that congenital anomalies and infections are the underlying causes. No discussion of the causes of functional enuresis or its rational treatment is included.

The Wilms tumor, or embryoma adenomyosarcoma, is the most common renal tumor in infants and children. Its treatment has never been satisfactory. The authors feel that immediate nephrectomy followed by high voltage roentgen therapy offers the best hope for a cure.

The text is well illustrated, with drawings of the various urologic surgical procedures. The treatment of such operable conditions in children as hypospadias and cryptorchidism is clearly and concisely stated.

Physiology of Micturition. By Orthello R. Langworthy, Laurence C. Kolb and Lloyd G. Lewis. Price, $3.50. Pp. 240, with 49 illustrations. Baltimore: Williams & Wilkins Company, 1940.

The title of this small book may mislead those who read only titles. The busy practitioner may put the book aside, assuming it is concerned purely with research and has no practical value. However, the subtitle, "Experimental and Clinical Studies with Suggestions as to Diagnosis and Treatment," describes the content more accurately, for the book is filled with aids to the clinical diagnosis and treatment of disturbances of bladder function resulting from neurologic disorders.

The authors, who are all well known in their respective fields, have done a vast amount of research on the bladder function of experimental animals and of man in health and in disease. Their cystometric studies on the measurement of intravesical pressures have furnished a scientific approach to the study of bladder function.

The book is concise and well organized. It is divided into six sections, which are concerned with such topics as the anatomic, pharmacologic and physiologic aspects of micturition, the relation of the peripheral nerves, the spinal cord and the brain to micturition and the clinical diagnosis of disorders of bladder function. Each section is composed of short chapters, and there is a brief paragraph of summary at the end of each chapter. There is an exhaustive bibliography.

The practicing pediatrician will not find a large amount of usable clinical material here, although there are references to enuresis and to the disturbances of bladder function associated with the various neurologic diseases. The book will be valuable to any one interested in gaining more than a superficial knowledge of the bladder and its function.

The Doctor and the Difficult Child. By Dr. William Moodie. Price, $1.50. Pp. 214, with no illustrations. New York: The Commonwealth Fund, 1940.

This is a good book, written by a psychiatrist who obviously has had a great deal of experience in a child guidance clinic (in London). It discusses the emotional problems of children in an interesting yet scientific manner.

In the first half of the book the proper methods of clinical examination are outlined and a valuable, detailed account is given of the technic to be used by the physician in determining the nature and the cause of behavior problems. The second part is concerned with such common psychiatric problems as stealing, lying, nervousness, backwardness, sexual difficulties, truancy, psychoses, disturbances in habits of sleeping or eating and mental deficiency.

The material is presented in an easily understandable manner. The book is free from psychiatric nomenclature; yet the descriptions are precise and accurate. This book should interest any one who works with problem children and should especially interest the pediatrician, the student and the social worker.

Melk in het bijzonder als zuigelingenvoedsel. By Dr. J. H. de Haas and Dr. O. Meulemans. Price, none given. Pp. 104, with 42 charts. Batavia: Drukkerij Smits, 1940.

This handbook is a collection of information about milk and related subjects for students and others interested in its use. There is no attempt to apply these facts to infant feeding, but tables and charts giving all necessary data for this purpose are included.

The general content, physical constituents, characteristics, bacteria, vitamins, enzymes and minerals of cow's milk, colostrum, breast milk, preserved liquid and

dry milks, special milks for infant feeding and milk products are given. The references from which much of this information was compiled are chiefly American.

This is a compact volume, thorough and complete, which should prove useful to any one concerned with infant feeding.

Clinical Practice in Infectious Diseases. By E. H. R. Harries and Maurice Mitman, with a foreword by W. Allan Daley. Price, $6. Pp. 468, with 31 illustrations. Baltimore: Williams & Wilkins Company, 1940.

This is a practical and complete textbook on infectious diseases. It is well written and contains no erroneous or superfluous information. The authors detail their personal experience. The discussion covers many new infectious diseases not ordinarily seen in contagious disease hospitals in America, such as Weil's disease, various louse-borne infections, glandular fever, psittacosis and infectious enteritis of children. It is up-to-date in every respect and even includes reference to sulfanilamide and allied drugs.

In addition to a complete index, there is a summary of each chapter, which is exceedingly helpful, since it permits reviewing of the contents of each single chapter at a glance.

All in all, it is my opinion that the book is one of the best texts on this subject.

The Story of Vitamin B_1. Compiled by C. R. Addinall, Ph.D. Revised edition. Price, none given. Pp. 72, with 18 illustrations. Rahway, N. J.: Merck & Co., Inc., 1940.

This revised review presents the significant results of the recent studies on vitamin B_1. Among the most interesting discoveries is the part vitamin B_1 plays in the formation of the enzyme cocarboxylase and the function of this enzyme. Surprising clinical results have been brought about by the use of massive doses of the vitamin in certain cases of ascites and edema associated with cardiac decompensation. Its toxicity has been shown to be so low that the danger from overdosage is nil. The role of the vitamin in plant physiology and culture is also presented. Each section carries abundant references, which enhance the value of the book for those wishing to consult original articles.

Psychiatric Social Work. By Lois Meredith French. Price, $2.25. Pp. 344, with 18 tables. New York: The Commonwealth Fund, 1940.

This book, which was sponsored by the American Association of Psychiatric Social Workers, deals with the development and importance of psychiatric social service. It describes the purpose and function of the psychiatric social worker, her position in the child guidance clinic and her relationship to the psychiatrist, to other social workers and to the community as a whole. Standards of training are discussed.

This book is well written by a competent worker in the field. It should prove helpful to public welfare organizations and to all persons who are interested in clinics and community or social projects, as well as to those who are interested in psychiatric work.

Hydrocephalus: Its Symptomatology, Pathology, Pathogenesis and Treatment. By Otto Marburg, M.D. Price, $3. Pp. 217, with 28 illustrations. New York: Oskar Piest, 1940.

While this book is not devoted exclusively to pediatrics, it includes a considerable amount of material on congenital hydrocephalus and other forms occurring in infancy and childhood. The whole volume is so well written and so excellently organized that the reviewer read it straight through from cover to cover without putting it down. The publisher should also be congratulated on the clear printing and general appearance of this little book. It would make an excellent gift.

Directory of Pediatric Societies

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
General Secretary: Dr. Kenneth D. Blackfan, 300 Longwood Ave., Boston.
Assistant Secretary-Treasurer: Dr. Charles F. McKhann, University of Michigan, Ann Arbor, Mich.

Canadian Committee:

Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. H. P. Wright, 1509 Sherbrooke St. W., Montreal.
Place: Boston. Time: Postponed indefinitely.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

British Paediatric Association

President: Prof. Charles McNeil, 44 Heriot Row, Edinburgh, Scotland.
Secretary: Dr. Arthur G. Maitland Jones, 31A Weymouth St., London, W. 1.

Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. E. Gjørup, Dronning Louises Børnehospital, Copenhagen.

Nederlandsche Vereeniging voor Kindergeneeskunde

President: Prof. Dr. J. van Lookeren Campagne, Hofstraat 16, Gröningen, Holland.
Secretary: Dr. R. P. van de Kasteele, Laan van Poot 340, 's Gravenhage, Holland.
Place: Different places. Time: Three times a year.

Paediatrický Spolok na Slovensku

President: Dr. A. J. C. Chura, Lazaretská 11, Bratislava.
Secretary: Dr. P. Rados, Lazaretská 6, Bratislava.
Place: Pediatric Clinic, University Bratislava. Time: Six times a year.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

ROYAL SOCIETY OF MEDICINE, SECTION FOR THE STUDY OF DISEASE IN CHILDREN

President: Dr. E. A. Cockayne, 98 Harley St., London, W. 1, England.
Secretary: Dr. R. Lightwood, 86 Brook St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

PALESTINE JEWISH MEDICAL ASSOCIATION, SECTION OF PHYSICIANS OF CHILDREN'S DISEASES

President: Prof. S. Rosenbaum, 26 Bialikstr., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

SOCIEDAD CUBANA DE PEDIATRÍA

President: Dr. Clemente Inclan Costa, Manrique 48, Habana.
Secretary: Dr. Serafin Falcon Lopez, Calle B No. 356, Vedado, Habana.
Place: Cátedra de Clinica Infantil, Hospital Mercedes, Habana. Time: Last Wednesday of every month.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Jorge Muñoz Turnbull, Av. Alvaro Obregón 186, Mexico, D. F.
Secretary: Dr. Fernando López Clares, Medellín 191, Mexico, D. F.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. B. Weill-Hallé, 49 Avenue Raymond Poincaré, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue du Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Malades, 49 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

URUGUAYAN SOCIETY OF PEDIATRICS

President: Dr. Conrado Pelfort, Av. 18 de Julio 1246, Montevideo.
Secretary: Dr. Héctor Mourigan, Av. 18 de Julio 2175, Montevideo.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. Julius H. Hess, 104 S. Michigan Ave., Chicago.
Secretary: Dr. Hugh L. Dwyer, 315 Alameda Rd., Kansas City, Mo.
Place: Cleveland. Time: June 2-6, 1941.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. Richard M. Smith, 66 Commonwealth Ave., Boston.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Statler Hotel, Boston. Time: Oct. 9-11, 1941.
Region I. Place: Hotel Taft, New Haven, Conn. Time: March 27-29, 1941.
Region II. Place: John Marshall Hotel, Richmond, Va. Time: April 24-25, 1941.
Region III. Place: Palmer House, Chicago. Time: May 15-17, 1941.
Region IV. Place: Fairmont Hotel, San Francisco. Time: May 1-3, 1941.

AMERICAN HOSPITAL ASSOCIATION, CHILDREN'S HOSPITAL SECTION

Chairman: Dr. D. L. Richardson, 593 Eddy St., Providence, R. I.
Secretary: Dr. Joelle C. Hiebert, 299 Main St., Lewiston, Maine.

AMERICAN PEDIATRIC SOCIETY

President: Dr. Thomas B. Cooley, 1728 Seminole Ave., Detroit.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid Ave., St. Louis.
Place: Hot Springs, Va. Time: May 22-24, 1941.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

President: Dr. L. M. Lindsay, 815 Medical Arts Bldg., Montreal.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, Hospital for Sick Children, Toronto.

SOCIETY FOR PEDIATRIC RESEARCH

President: Dr. A. Ashley Weech, 3975 Broadway, New York.
Secretary: Dr. Mitchell I. Rubin, 1740 Bainbridge St., Philadelphia.
Place: Chalfonte-Haddon Hall Hotel, Atlantic City, N. J. Time: May 6-7, 1941.

SECTIONAL

INTERMOUNTAIN PEDIATRIC SOCIETY

President: Dr. Eugene Smith, 385–24th St., Ogden, Utah.
Secretary-Treasurer: Dr. W. C. Cheney, 837 Boston Bldg., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

NEW ENGLAND PEDIATRIC SOCIETY

President: Dr. R. Cannon Eley, 319 Longwood Ave., Boston.
Secretary-Treasurer: Dr. James Marvin Baty, 319 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

NORTH PACIFIC PEDIATRIC SOCIETY

President: Dr. S. G. Henricke, 4215 N. E. Hancock St., Portland, Ore.
Secretary: Dr. J. S. Backstrand, 333 Wyatt Court, Salem, Ore.
Place: Doernbecker Hospital and University of Oregon Medical School, Portland. Time: Jan. 25, 1941.

ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. Donn Barber, 802½–8th Ave., Greeley, Colo.
Secretary: Dr. Kenneth Schmidt, Republic Bldg., Denver.
Place: Children's Hospital, Denver. Time: First Saturday of each month from September to May, inclusive, 7:30 p. m.

SOUTHERN MEDICAL ASSOCIATION, SECTION OF PEDIATRICS

Chairman: Dr. Harvey F. Garrison, 319 E. Capitol St., Jackson, Miss.
Secretary: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables, Fla.

STATE

ALABAMA PEDIATRIC SOCIETY

President: Dr. M. V. Adams, 803 Government St., Mobile.
Secretary-Treasurer: Dr. William R. Britton, 4 Catoma St., Montgomery.

ARKANSAS STATE PEDIATRIC ASSOCIATION

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

CALIFORNIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. William Belford, 233 A St., San Diego.
Secretary: Dr. John J. Miller Jr., 2398 Sacramento St., San Francisco.
Place: Del Monte. Time: May 1941.

Florida State Pediatric Society

President: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables.
Secretary: Dr. George N. Leonard, 605 Lincoln Rd., Miami Beach.
Place: Concurrent with state association meeting at time of convention.

Georgia Pediatric Society

President: Dr. R. C. McGahee, 1345 Greene St., Augusta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. D. C. Darrow, 789 Howard Ave., New Haven.
Secretary: Dr. Joseph L. Hetzel, 103 N. Main St., Waterbury.
Time: Three meetings a year.

Illinois State Medical Society, Section on Pediatrics

Chairman: Dr. Orville Barbour, 331 Fulton St., Peoria.
Secretary: Dr. Craig Butler, 715 Lake St., Oak Park.
Place: Chicago. Time: May 1941.

Indiana State Pediatric Society

President: Dr. K. T. Knode, 1105 E. Jefferson Blvd., South Bend.
Secretary-Treasurer: Dr. Mathew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

Iowa Pediatric Society

President: Dr. Morgan J. Foster, 837 Higley Bldg., Cedar Rapids.
Secretary-Treasurer: Dr. Arnold M. Smythe, 406–6th Ave., Des Moines.

Louisiana State Pediatric Society

President: Dr. H. Aubrey White, Alexandria.
Secretary-Treasurer: Dr. W. C. Rivenbark, 3503 Prytania St., New York.
Place: Shreveport. Time: April 1941.

Medical Society of State of New York, Section on Pediatrics

Chairman: Dr. Norman L. Hawkins, 11 Public Sq., Watertown, N. Y.
Secretary: Dr. William J. Orr, 135 Linwood Ave., Buffalo.

Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. John D. Sturgeon Jr., 22 N. Gallatin Ave., Uniontown.
Secretary: Dr. Elwood W. Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Place: Pittsburgh. Time: Sept. 29-Oct. 2, 1941.

Michigan State Medical Society, Pediatric Section

Chairman: Dr. Harry Towsley, University of Michigan Hospital, Ann Arbor.
Secretary: Dr. Leon DeVel, 110 E. Fulton, Grand Rapids.

Mississippi State Pediatric Society

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.
Place: Biloxi. Time: May 12. 1941.

Nebraska Pediatric Society

President: Dr. J. C. Iwersen, 236 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. Elmer W. Bantin, 440 Aquila Court Bldg., Omaha.
Place: As announced by Committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NEW HAMPSHIRE PEDIATRIC SOCIETY

President: Dr. MacLean J. Gill, 14 N. State St., Concord.
Secretary-Treasurer: Dr. Ursula G. Sanders, 46 Pleasant St., Concord.
Time: Twice yearly.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Marion Y. Keith, 369 N. Elm St., Greensboro.
Secretary: Dr. G. W. Kutscher Jr., 176 Woodfin St., Asheville.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. Ben H. Nicholson, 301 N.W. 12th St., Oklahoma City.
Secretary: Dr. Luvern Hays, 108 W. 6th St., Tulsa.
Place: Oklahoma Club. Time: 6:30 p. m., fourth Friday of each alternate month from September to May, inclusive.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. R. B. Josey, 1517 Hampton Ave., Columbia.
Secretary-Treasurer: Dr. Wilson Ball, South Carolina State Health Dept., Columbia.

TENNESSEE STATE PEDIATRIC SOCIETY

President: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis.
Secretary: Dr. Gilbert Eblen, 611 W. Main Ave., Knoxville.

TEXAS PEDIATRIC SOCIETY

President: Dr. C. P. Jasperson, 509 Nixon Bldg., Corpus Christi.
Secretary-Treasurer: Dr. F. H. Lancaster, 4409 Fannin St., Houston.
Place: Fort Worth. Time: May 14, 1941.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. John M. Bishop, 511 Medical Arts Bldg., Roanoke.
Secretary: Dr. Edwin A. Harper, 301 Rivermont Ave., Lynchburg.

WEST VIRGINIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

President: Dr. Theresa O. Snaith, 450 Center Ave., Weston.
Secretary: Dr. Henrietta L. Marquis, 211 Bair Bldg., Beckley.

LOCAL

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION

Chairman: Dr. J. D. Nourse, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. I. B. Silber, 10465 Carnegie Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time: October, December, February and April.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. I. Nelles Silverthorne, 170 St. George St., Toronto, Canada.
Secretary: Dr. G. P. Hamblin, 2333 Bloor St. W., Toronto, Canada.

BRONX PEDIATRIC SOCIETY

President: Dr. David Greene, 910 Grand Concourse, New York.
Secretary: Dr. F. E. Chick, 2325 University Ave., New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Every second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. John A. Monfort, 861 Carroll St., Brooklyn.
Secretary: Dr. Walter Coles, 604–2d St., Brooklyn.
Place: Kings County Medical Society Bldg. Time: Fourth Wednesday of each month, except May, June, August and September.

Central New York Pediatric Club

President: Dr. Frank van der Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Places: Various cities in New York. Time: Third Tuesday of April and September.

Chicago Pediatric Society

President: Dr. Philip Rosenblum, 2376 E. 71st St., Chicago.
Secretary: Dr. A. L. Newcomb, 1791 W. Howard St., Chicago.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, inclusive.

Dallas Pediatric Society

President: Dr. Edgar Loomis, 351 W. Jefferson Ave., Dallas, Texas.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmont Ave., Dallas, Texas.
Place: Bradford Baby Hospital. Time: 1 p. m., second and fourth Saturdays of each month.

Detroit Pediatric Society

President: Dr. Robert J. Mason, 460 Birmingham Rd., Birmingham, Mich.
Secretary: Dr. J. Hugh Lewis, 2966 Biddle Ave., Wyandotte, Mich.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month from October to June, inclusive.

Fulton County Medical Society, Pediatric Section (Atlanta, Ga.)

Chairman: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Secretary: Dr. Harry Lange, 478 Peachtree St. N. E., Atlanta.
Place: Academy of Medicine, 38 Prescott St. N. E. Time: Second Thursday of each month from October to April, 8 p. m.

Houston Pediatric Society

President: Dr. Thomas J. Donovan, 3820 Fannin St., Houston, Texas.
Secretary: Dr. Raymond Cohen, 2300 Caroline St., Houston, Texas.
Place: Houston Club. Time: Third Monday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. John Aull, 1103 Grand Ave., Kansas City.
Secretary: Dr. George Herrman, 1107 Bryant Bldg., Kansas City.
Place: Kansas City General Hospital. Time: On call.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Alonzo Cass, 1908 Wilshire Blvd., Los Angeles.
Secretary-Treasurer: Dr. Gladys Patric Shahovitch, 3936 Roderick Rd., Los Angeles.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

MEDICAL SOCIETY OF THE COUNTY OF KINGS AND THE ACADEMY OF MEDICINE OF BROOKLYN, PEDIATRIC SECTION

President: Dr. Sydney Nussbaum, 247 Ocean View Ave., Brooklyn.
Secretary: Dr. Harry Bikoff, 850 St. Marks Ave., Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., second Monday of each month, October to March, inclusive.

MEDICAL SOCIETY OF THE COUNTY OF QUEENS, INC., SECTION ON PEDIATRICS

Chairman: Dr. A. A. Trivilino, 88-07–150th St., Jamaica, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144–38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA, SECTION ON PEDIATRICS

President: Dr. Harry A. Ong, 1801 I St. N. W., Washington, D. C.
Secretary-Treasurer: Dr. William F. Burdick, 5402 Connecticut Ave. N. W., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., fourth Thursday of every month.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. E. C. Mitchell, 1073 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry Jacobson, 1193 Madison Ave., Memphis, Tenn.
Place: John Gaston Hospital. Time: Quarterly.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. R. P. Schowalter, 411 E. Mason St., Milwaukee.
Secretary-Treasurer: Dr. George H. Wegmann, 2650 W. Hopkins St., Milwaukee.
Place: Children's Hospital. Time: Second Wednesday of each alternate month, beginning with February.

NEW YORK ACADEMY OF MEDICINE, SECTION OF PEDIATRICS

Chairman: Dr. Leslie O. Ashton, 850 Park Ave., New York.
Secretary: Dr. Alfred Langmann, 108 E. 68th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

NORTHERN CALIFORNIA AFFILIATES

President: Dr. Crawford Bost, 490 Post St., San Francisco.
Secretary: Dr. William A. Reilly, 384 Post St., San Francisco.
Time: Second Thursday of September, November, January, March and May.

NORTHWESTERN PEDIATRIC SOCIETY

President: Dr. Harold Flanagan, 711 Lowry Medical Arts Bldg., St. Paul, Minn.
Secretary-Treasurer: Dr. George B. Logan, Mayo Clinic, Rochester, Minn.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

OKLAHOMA CITY PEDIATRIC SOCIETY

President: Dr. J. Byron Snow, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. G. R. Felts, 1200 N. Walker St., Oklahoma City.
Place: Oklahoma Club. Time: Fourth Friday of each alternate month.

Philadelphia Pediatric Society

President: Dr. Philip S. Barba, 222 W. Harvey St., Germantown, Pa.
Secretary: Dr. Aims C. McGuinness, Children's Hospital, 1740 Bainbridge St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday of each month from October to April, inclusive.

Pittsburgh Pediatric Society

President: Dr. E. L. Piper, 3200–5th Ave., Pittsburgh.
Secretary-Treasurer: Dr. Carl Ruder, 646 Washington Rd., Mount Lebanon, Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate month from October to June, inclusive.

Richmond Pediatric Society

President: Dr. Louise Fry Galvin, 214 S. Boulevard, Richmond, Va.
Secretary-Treasurer: Dr. Herman W. Farber, 501 E. Franklin St., Richmond, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: 8 p. m., third Thursday of each month, except June, July and August.

Rochester Pediatric Society

President: Dr. David Wolin, 16 N. Goodman St., Rochester, N. Y.
Secretary: Dr. W. L. Bradford, 16 N. Goodman St., Rochester, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee. Time: Third Friday of each month from October to May.

St. Louis Pediatric Society

President: Dr. Max Deutch, 634 N. Grand Blvd., St. Louis.
Secretary-Treasurer: Dr. Peter G. Danis, 634 N. Grand Blvd., St. Louis.
Place: St. Louis Medical Society Bldg. Time: First Friday of each month from October to June.

Seattle Pediatric Society

President: Dr. Jay I. Durand, 1305–4th Ave., Seattle.
Secretary: Dr. Frederick B. Joy, 1215–4th Ave., Seattle.
Place: College Club. Time: Third Friday of each month, 6:30 p. m.

Southwestern Pediatric Society

President: Dr. Norman Nixon, 1136 W. 6th St., Los Angeles.
Secretary: Dr. Donald C. Shelby, 3780 Wilshire Blvd., Los Angeles.
Place: Jonathan Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Campbell Harvey, 35 W. Huron St., Pontiac, Mich.
Secretary: Dr. Harry A. Towsley, University of Michigan, Department of Pediatrics and Communicable Diseases, Ann Arbor, Mich.
Time: Autumn, 1941.

Westchester County Medical Society, Pediatric Section (New York)

President: Dr. John B. Ahouse, 27 Ludlow St., Yonkers, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye.
Place: Grasslands Hospital, Valhalla, N. Y. Time: Third Thursday in October, December, February and April.